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Physiologic and Endocrine Correlates of Overweightness in African Americans and Caucasians

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14. ABSTRACT
Obesity has reached epidemic levels and the incidence continues to rise. The current study was seeking to examine the hypothesis that obesity may reflect dysfunctioning of the hypothalamic-pituitary-adrenal (HPA) axis in response to stressors. African American persons are at greatest risk, but reasons for this difference are unknown. We studied 126 healthy men and women of Caucasian (CA) and African American (AA) ethnicity and examined their responses to physiologic stressors: exercise and ingestion of a meal. **Methods:** The HPA axis was studied by using two stress paradigms and two steroid regimens: hydrocortisone (HCO) and dexamethasone (DEX). We were able to detect subtle differences in HPA axis reactivity in obese individuals that might contribute to morbidity and perhaps even make individuals resistant to therapeutic interventions. **Results:** AA, particularly those who are obese by percent body fat, are highly sensitive to glucocorticoids. This was noted during exercise under conditions of DEX and in response to a meal, under all conditions but to a greater extent under conditions for DEX. Importantly, AA had significantly lower cardiovascular fitness than CA. Fitness was inversely related to obesity, insulin resistance, and glucocorticoid sensitivity. Lastly, lipid profiles of AA are more favorable that age-matched, healthy CA. Using either triglycerides or HDL-cholesterol as indicators of cardiovascular disease would indicate minimal risk. **Conclusions:** Over the past five years, we achieved all goals for this project. Notably, we enrolled 160 participants and completed testing on 126. In addition, nine abstracts were submitted and we presented our physiological, biochemical, and psychological results on multiple occasions. We have prepared five manuscripts on the following topics: stress coping style and insulin resistance; psychological and physiological correlates of insulin resistance at fasting and response to a meal in AA and CA; ethnic-specific criteria for metabolic syndrome in African Americans; cardiorespiratory risk factors for African Americans and Caucasians; and, triglycerides and HDL as surrogates for Insulin Resistance. Two of the five manuscripts were published and three are under review. Several more will be prepared over the next year.

15. SUBJECT TERMS
obesity, insulin sensitivity, glucocorticoids, metabolic syndrome, African Americans, Caucasians, exercise, meal feeding

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INTRODUCTION

Obesity has reached epidemic levels and yet the incidence continues to rise. The current study is seeking to examine the hypothesis that obesity may reflect a dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis in response to stressors. African American persons are at greatest risk, but reasons for this difference are unknown. We are studying 126 men and women of Caucasian (CA) and African American (AA) ethnicity to examine their responses to physiologic stressors: exercise and ingestion of a meal.

BODY

Year Five:

1. *Recruit, screen, and test 1Overweight/Obese and 3 Non-obese subjects*

Table 1 presents the participants recruited and tested over the past year.

Table 1. Breakdown of Normal/Overweight/Obese Participants by Ethnicity (Year 5)

Normal (NW) Overweight (OW) & Obese (OB)	CA-NW	AA-NW	CA-OW	AA-OW	CA-OB	AA-OB	TOTAL
Screened	0	0	0	0	0	0	**0**
Recruited/Enrolled	0	0	0	0	0	0	**0**
In Progress	0	0	0	0	0	0	**0**
Dropped	0	1	0	0	0	0	**1**
Completed	**0**	**2**	**0**	**0**	**0**	**1**	**3**

2. *Complete subject recruitment*

Since the start of the study, we have recruited 160 subjects. Of those, 126 subjects have completed the study; 33 have dropped out (Table 2). We have over recruited AA in every weight class as expected, but because the hormonal data suggest that some subjects did not take the prescribed treatments, we have increased our accrual in selected cells. With only 4 subjects remaining in the study from the last annual review, we successfully completed 3 of the 4 subjects; one subject was excluded from the study due to health issues.

For the past three years (March 2006, June 2007, March 2008), we provided body composition services and health consultations as community service and as a recruitment tool at the Montgomery County Heart Health Symposium for African Americans in Germantown, MD.

Years 1-5 Subject Recruitment and Progress

		Normal	Overweight	Obese	Total
A	**Enrolled**	34	37	38	109
	In Progress	0	0	0	0
	Completed	24	28	26	78
	Dropped	9	10	12	31
	Needed	**0**	**0**	**0**	**0**
CA	**Enrolled**	18	16	17	51
	In Progress	0	0	0	0
	Completed	16	16	16	48
	Dropped	2	0	1	3
	Needed	**0**	**0**	**0**	**0**
	Total in Progress	0			
	Total Completed	126			
	Total Needed	0			

3. *Complete subject testing*

We have completed testing 126 subjects.

4. *Evaluate, reduce, and analyze data*

Multiple meetings have occurred among the PI, Co-investigators, with the Project Coordinator and other key staff on a monthly basis to discuss issues and examine data collected on all completed subjects. Hormone, psychological, and other physiological data have been completed and much of the data have been analyzed.

5. *Biochemical analyses.*

Radioimmunoassay (RIA) and ELISA analyses have been completed for all of the different hormones of interest. Specifically, we have competed data on ACTH, Insulin, Cortisol (CORT), DHEA, and DHEAS, as well as blood lipid profiles and C-reactive protein.

6. *Statistical analyses on ethnicity/obesity and potential interactions.*

We have complete data on 126 subjects and Table 3 presents basic demographic and anthropometric data for the groups by ethnicity and body mass index (BMI) category. From data analyses, age, weight, BMI, and maximal aerobic capacity were significantly different across weight groups. In contrast, fasting blood glucose was not significantly different between AA and CA. Despite similar weights and BMI, maximal aerobic capacity (VO_{2max}) was significantly lower in AA than CA (Table 3). Overall, VO_{2max} was 42.5 ± 10.1 ml/kg/min for CA and 36.7 ± 10.3 ml/kg/min for AA, ($p = 0.00$. The values for AA are very low relative to normative data and indicate poor to fair cardiovascular fitness.

Table 2.   Characteristics and Physiological Measures by Ethnicity and Weight Group

	CA-NW (n=16)	CA-OW (n=16)	CA-OB (n=12)	AA-NW (n=20)	AA-OW (n=26)	AA-OB (n=21)
Age (yrs)	24.7 ± 5.0	29.9 ± 3.8	30.7 ± 5.6	27.4 ± 7.2	31.9 ± 8.9	33.3 ± 7.8
Weight (kg)	63.2 ± 9.1	85.4 ± 8.7	103.4 ± 10.8	64.0 ± 10.1	81.6 ± 11.6	94.4 ± 12.8
BMI (kg/m^2)	22.1 ± 1.6	27.1 ± 1.5	33.7 ± 2.4	22.4 ± 1.5	27.4 ± 1.5	32.7 ± 2.2
VO$_{2max}$ (ml/kg/min)	48.1 ± 8.2	43.5 ± 8.4	35.6 ± 9.6	41.9 ± 9.8	39.2 ± 9.2	28.9 ± 7.3
Glucose (mmol/L)	5.1 ± 0.6	5.4 ± 0.7	5.5 ± 0.6	5.1 ± 0.8	5.2 ± 0.7	5.4 ± 1.0

Values are mean ± SD.

7.   *Reduce and interpret data on HPA reactivity from the exercise and meal challenge tests as a function of ethnicity and obesity after all subjects have been tested.*

Figure 1 presents the patterns of change in ACTH and cortisol in response to exercise as a function of BMI category. Mean peak ACTH and cortisol concentrations are lower in overweight and obese participants compared to normal weight controls.

Figure 1. Plasma ACTH and Cortisol Responses to Exercise over Time by BMI
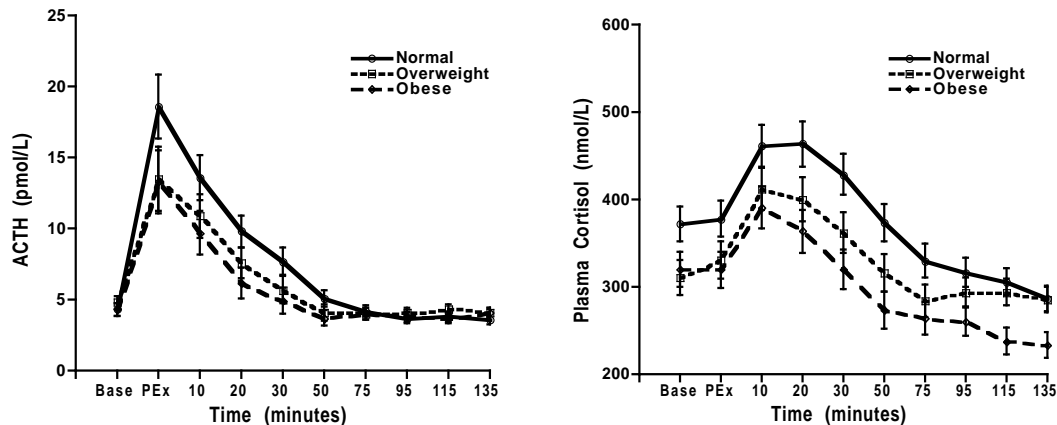
Areas under the curve (AUC) for the exercise challenge and the meal challenge were calculated for ACTH and CORT (n = 46 CA, 67 AA) responses. Analyses of the data showed higher ACTH and CORT for CA in response to exercise as compared to AA (Table 3). Within exercise and BMI class, only CA had a significantly higher response in CORT levels. The HPA axis was not activated by the meal and did not differ by either ethnicity or weight category.

Table 3.   Areas Under the Curve for ACTH and CORT after Exercise Challenge

	ACTH (pM•1.2 hr)	CORT (nM•135 min)
AA	8.3 ± 0.7	337.6 ± 12.9
CA	9.5 ± 1.0	410.2 ± 18.3*

Values are mean ± SE. *p = 0.001

8. *Reduce and interpret data describing relationship between HPA axis resistance to feedback control and insulin resistance as a function of obesity and ethnicity after all subjects have been tested.*

Insulin resistance (IR) was calculated from fasting serum insulin by using HOMA [(glucose (mmol/L) x insulin (µIU/mL))/22.5] for 99 AA and 50 CA (Figure 2). Individuals with a higher BMI had a greater IR. Differences were found among BMI groups, with the OB group having significantly higher values than NW and OW groups. Although no ethnic differences were noted for HOMA, fasting insulin was significantly higher in AA compared to CA (data not shown).

Figure 3 presents insulin and glucose responses to Hydrocortisone (HCO), Dexamethasone (DEX), and Placebo (PLA) by BMI category. DEX increased glucose and insulin levels in all weight groups (Figure 3 dashed lines), whereas HCO (dotted lines) only affected the insulin response in the Obese group: insulin was increased by HCO, but with no accompanying changes in glucose.

Figure 2. Insulin Resistance by HOMA by BMI and Ethnicity
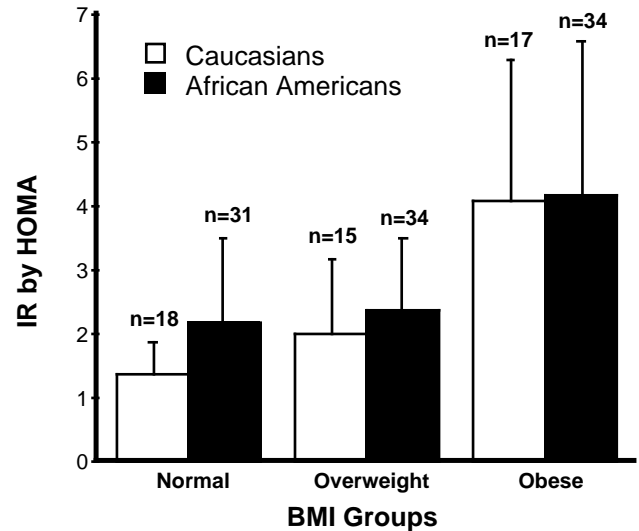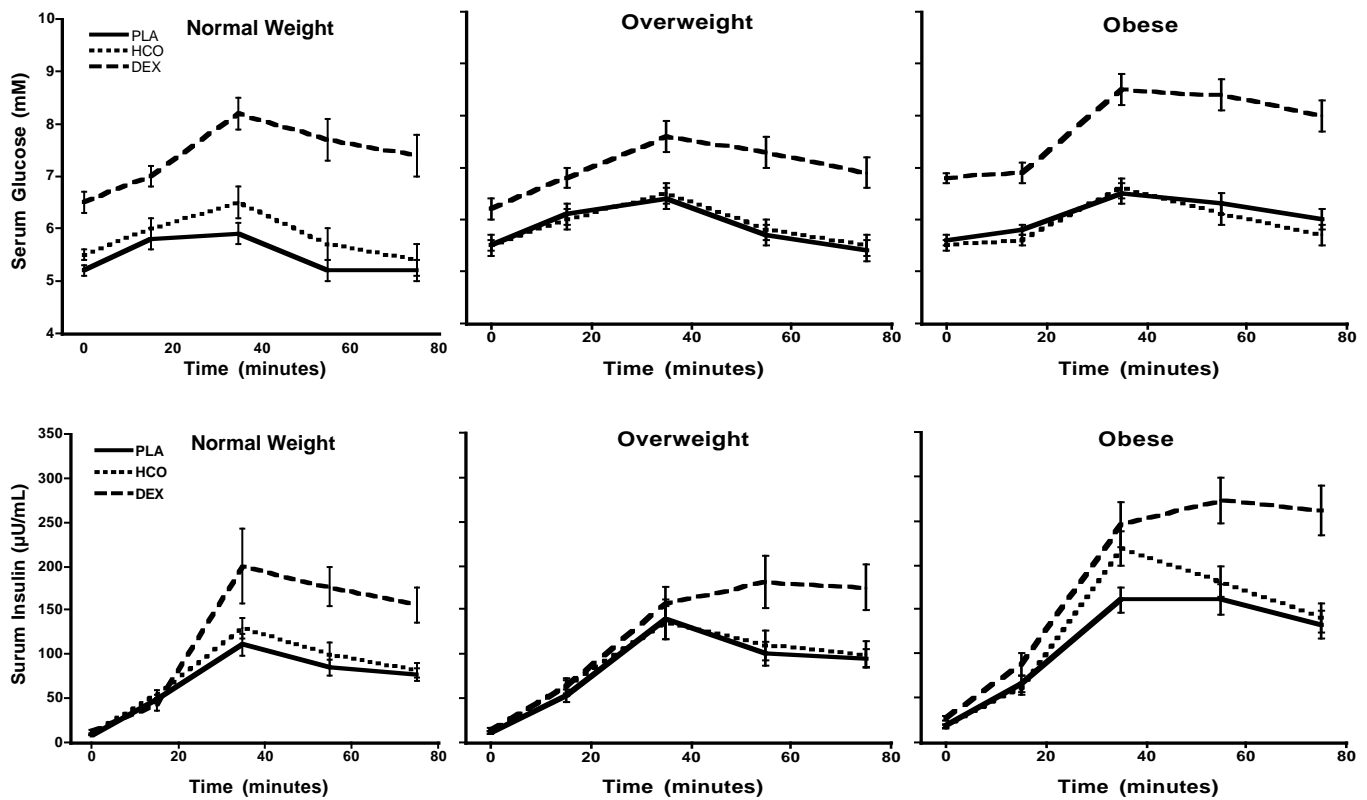

Figure 3. Serum Glucose and Insulin by BMI and Treatment after a Meal

9.   *Reduce and interpret data describing relation between exercise-associated increases in insulin and glucocorticoid sensitivity as a function of ethnicity.*

Table 4 presents the AUCs for insulin during the meal challenge by ethnicity and BMI. Significant ethnic differences were noted across all three treatment groups: AA secreted more insulin than CA for every treatment condition. Likewise, significant differences were noted for BMI across all treatments, with the OB group releasing significantly greater amounts of insulin than NW and OW. When analyzed within ethnicity by BMI, significant differences were noted for CA by HCO and PLA and for AA by all three Treatments.

Table 4.   Treatment Effects on Insulin AUC (µIU/mL/70min) by ethnicity and BMI after a Meal

Group	n	HCO	DEX	PLA
AA *	77	9,415 ± 693*	13,919 ± 1106*	8,670 ± 596*
CA	48	6,298 ± 560	8,316 ± 703	5,024 ± 465
AA NW	23	6,704 ± 912	12,823 ± 2089	6,283 ± 784
AA OW	28	10,305 ± 1630	13,973 ± 2115	9,490 ± 1317
AA OB	26	11,586 ± 1162	17,972 ± 2041	10,458 ± 995
CA NW	16	5,639 ± 702	7509 ± 658	4,488 ± 522
CA OW	16	4,198 ± 558	6,934 ± 1151	3,836 ± 600
CA OB	16	9,074 ± 1254	11,258 ± 1678	7,259 ± 1130

Values are mean ± SE. * $p < 0.05$

Figure 4 depicts the ratios of AUCs for insulin to glucose by treatment condition and ethnicity. Significant ethnic differences were noted across all treatments, such that AA had significantly greater increases in insulin relative to blood glucose levels. Figure 5 presents the patterns of change in insulin by ethnicity and treatments. Despite no significant ethnic differences in plasma glucose levels (data not shown), AA released significantly more insulin in response to the same meal challenge (Figure 5). It is important to note, that data from some participants had unusually high cortisol values relative to the rest of the subjects after taking DEX (a value < 5 µg/dl or 138 nM is expected after taking 4 mg of DEX), thus we tested for DEX levels and concluded that several participants did not take Treatment 2. Such subjects were excluded from these particular analyses.
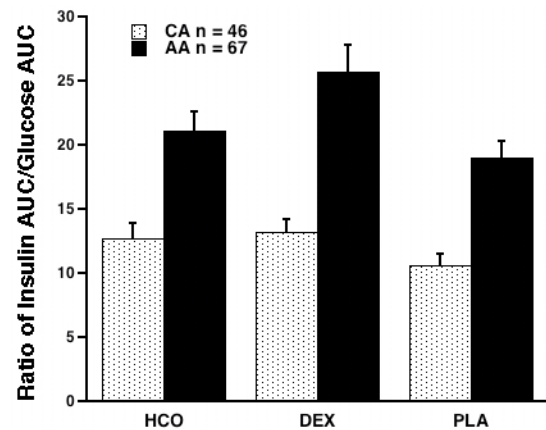

Figure 4. Ratio of AUC for Insulin to Glucose after a Meal

AUCs for CORT over the course of the exercise challenge were calculated. Figure 6 depicts these AUCs as a function of obese vs. non-obese, ethnicity, and the interactions of obesity and ethnicity. The upper left figure demonstrates that obese individuals (based on percent body fat rather than BMI) had significantly blunted CORT responses to exercise under conditions of HCO and Placebo. Likewise, the upper right figure shows that CA had significantly greater responses to exercise than AA under the same condition. In contrast, a significant obesity X ethnicity interaction was noted for DEX, such that obese AA were highly sensitive to DEX and had lower AUCs than obese CA whereas non-obese AA had higher values than non-obese CA. Thus, obese AA (n = 49) are highly sensitive to cortisol, particularly with regard to the Type II glucocorticoid receptors. This in part may explain the exaggerated insulin responses in obese AA.
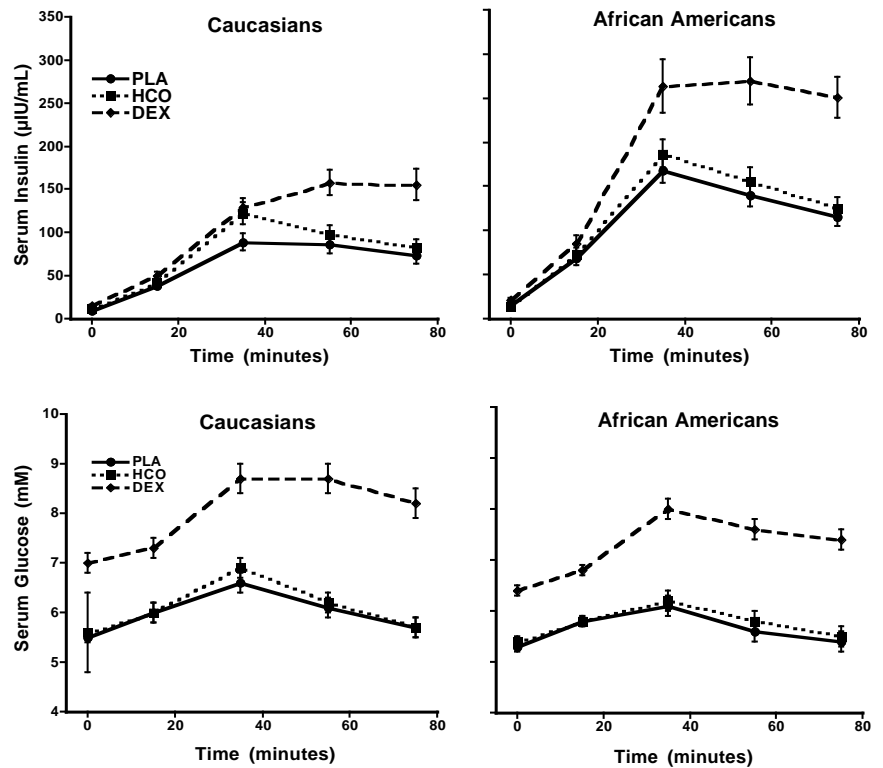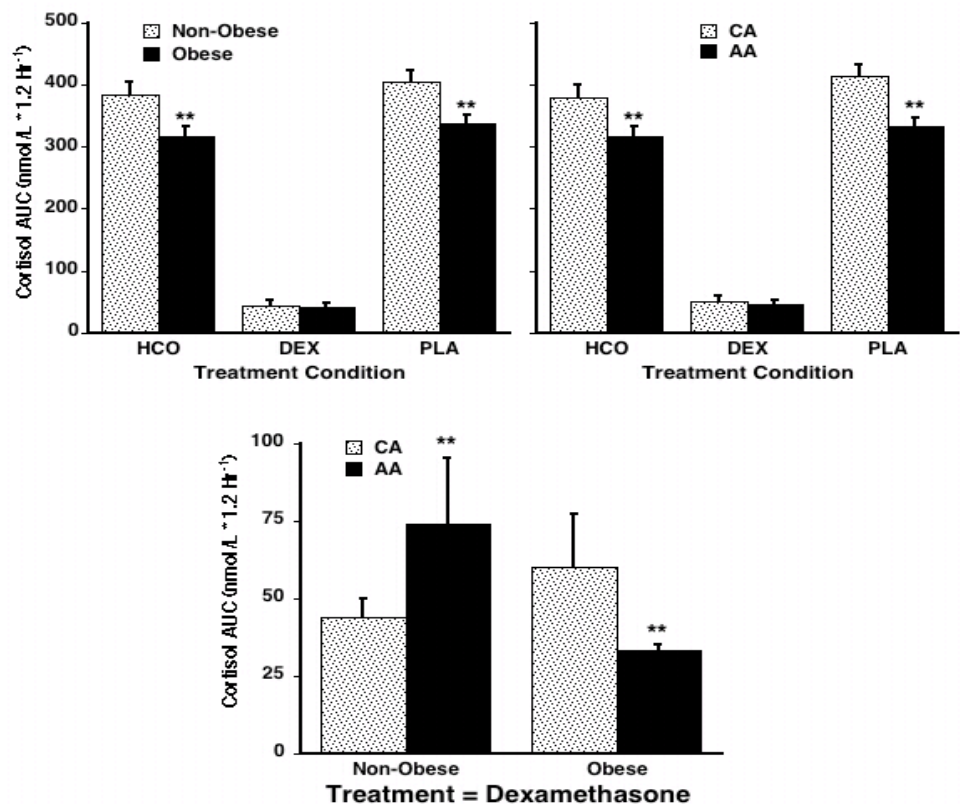

Figure 5. Serum Insulin (µIU/mL) and Serum Glucose (mM) over Meal Time Glucose (mM)

Figure 6. AUC CORT (nM*1.2Hr^{-1}) over an Exercise Challenge

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10. *Examine data as a function of gender after testing 73 men and 78 women.*

Expected gender differences were found in the preliminary data analyses between men and women. Men had a greater maximal aerobic capacity (VO_{2max}) (Men: 43.8 ± 8.9 vs. Women 34.2 ± 9.6 ml/kg/min), larger waist circumference (Men: 91.2 ± 12.0 vs. Women: 84.8 ± 13.6 cm), and lower percent body fat (Men: 26.1 ± 6.0 vs. Women: 36.9 ± 7.4 %) than women.

Significant gender differences were also noted with regard to stress reactivity and the magnitude of the response to exercise, particularly under conditions of HCO and PLA. Figure 7 presents the ACTH and CORT responses by gender for all treatment groups.
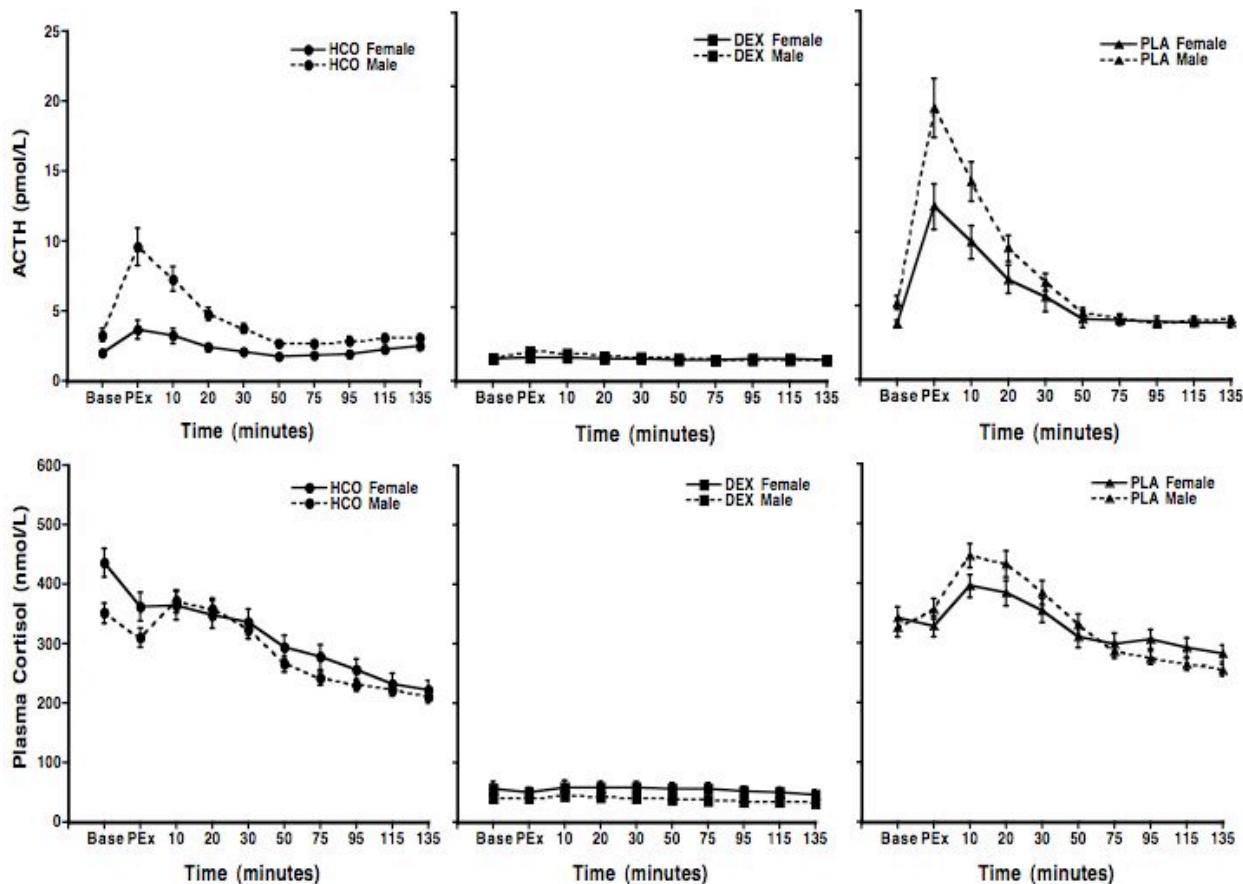

Figure 8 presents gender differences for selected psychological variables on the Stress Profile and the Beck Depression Inventory (BDI) questionnaire. Although women had significantly higher self-reported scores for stress, they also reported having greater social support network than men. Men reported participating in risky behaviors more frequently than women. Men also had significantly lower scores on the BDI (Men: 2.9 ± 0.4 vs. Women: 5.0 ± 0.4) as compared to women. The trend for greater coping strategies among women through social support may offset their negative feelings of stress and depression.
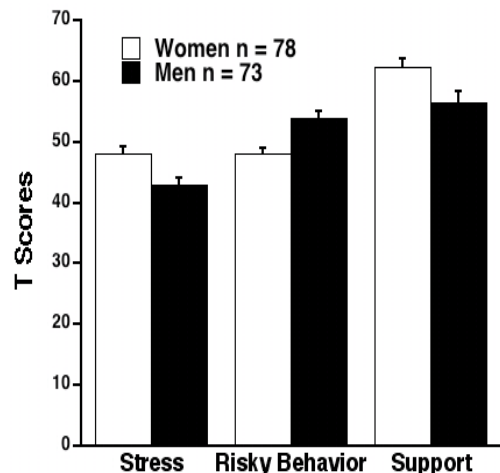

Figure 8. Stress Profile Responses by Gender

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KEY RESEARCH ACCOMPLISHMENTS

- No significant differences were found between AA and CA in the measurements of weight (AA: ± vs. CA: ± kg), BMI (AA: 27.8 ± 4.5 vs. CA: 27.6 ± 5.2 kg/m^2), waist circumference (AA: 88.0 ± 12.1 vs. CA: 88.2 ± 15.2 cm), and fasting plasma glucose (AA: 5.2 ± 0.9 vs. CA: 5.3 ± 0.7 mmol/L).
- Maximal aerobic capacity (V0$_{2max}$) was significantly lower in AA than CA (36.7 ± 10.3 and 42.5 ± 10.1 ml/kg/min for AA and CA, respectively) [$F_{(1,140)} = 10.6$, $p = 0.001$].
- Insulin Resistance (IR) by HOMA (µIU/mL x mmol/L) was significantly higher in Obese (4.2 ± 0.33) compared to Normal (1.9 ± 0.16) and Overweight (2.3 ± 0.16).
- Fasting glucose and insulin by HOMA IR differed significantly by BMI category [$F_{(2,148)} = 27.9$, $p < 0.001$].
- In AA: IR was positively correlated with BMI ($r = 0.46$) and hip-waist ratio ($r = .18$) and negatively correlated to VO$_{2max}$ ($r = -0.34$).
- Waist circumference was predictive of fasting insulin in CA ($r=0.720$) but not AA ($r=0.381$)
- In CA: IR was positively correlated with BMI ($r = 0.72$), hip-waist ratio ($r = 0.30$), and body fat percent ($r = .57$); and negatively correlated with VO$_{2max}$ ($r = -0.56$).
- Cardiovascular fitness was significantly and inversely related to percent fat in both CA (-0.851) and AA (-0.700).
- Morning basal ACTH concentrations were comparable in CA and AA, but morning cortisol concentrations were significantly lower in AA than CA [$F_{(1,124)} = 19.34$, $p < 0.001$].
- Peak ACTH response to exercise did not differ significantly by ethnicity: AA: 22.4 ± 2.3 vs. CA: 29.2 ± 3.3; in contrast, AA had significantly blunted cortisol responses compared to CA [$F_{(1,111)} = 23.8$, $p < 0.001$].
- Glucose levels after a liquid meal did not differ between AA and CA, but insulin responses were significantly higher in AA [$F_{(1,148)} = 7.328$, $p = 0.008$; AUC -$F_{(1,147)} = 10.119$, $p = 0.002$].
- Women reported significantly higher scores for stress (Women: 48.1 ± 1.3 vs. Men: 43.0 ± 1.0) than men [$F_{(1,149)} = 9.603$, $p = 0.002$].
- Men had significantly higher scores for participating in risky behaviors (Men: 54.01 ± 1.1 vs. Women: 48.09 ± 1.0) than women [$F_{(1,150)} = 2.912$, $p = 0.005$].
- Men also had significantly lower scores on the Beck Depression Inventory (Men: 2.9 ± 0.4 vs. Women: 5.0 ± 0.5) as compared to women [$p = 0.003$].
- AA men and women have more favorable triglyceride measures and HDL measures than CA: Triglycerides (CA Men: 110.4 ± 58.6, Women: 106.0 ± 59.3 vs. AA Men: 83.4 ± 44.6, Women: 55.3 ± 37.5); and, HDL (CA Men: 35.9 ± 6.5, Women: 49.5 ± 11.3 vs. AA Men: 42.2 ± 10.9, Women: 50.9 ± 12.3).
- C-Reactive Protein levels were significantly negatively related to aerobic fitness ($r = -0.414$; $p < 0.001$) and positively related to percent body fat ($r= 0.486$, $p < 0.00$).

REPORTABLE OUTCOMES 2006-2009

Abstracts

1.   Kim-Dorner SJ, Poth M, Deuster PA and Remaley AT. Triglycerides and HDL as Surrogates for Insulin Resistance. Accepted for presentation at the Endocrine Society 2009.

2.   Frazier, B, Hsiao CW, Davis JL, Remaley AT, Deuster PA and Poth M. Dehydroepiandrosterone and Determinates of Insulin Resistance in African American Women. Accepted for presentation at the Endocrine Society 2009.

3.   Deuster PA, Zeno SA, Kim-Dorner SJ, Poth M. Psychological and Physiological Contributors Correlates of Obesity and Insulin Resistance in African-Americans and Caucasians. Submitted to Military Health Research Forum, February 2009.

4.   Frazier, B. Dehydroepiandrosterone and Determinants of Insulin Resistance in African-American Women. Accepted at Uniformed Services Pediatrics Section in September 2008. 2nd Place Winner.

5.   Abraham PA, McGill C, Davis J, Zeno SA, C, Deuster PA and Poth M. Physiological Correlates of the Insulin Response to a Test Meal in African American and Caucasian Women. Presentation at The Endocrine Society 2008.

6.   Kim SJ, Oates C, Fendrick N, Zeno S, Faraday M, Sbrocco T, Poth M, and Deuster P. Physiological and Psychological Correlates of Insulin Resistance in African Americans and Caucasians. Presented at the Society for Behavioral Medicine 2006.

7.   Fendrick N, Stephens Q, Oates C, Kim S, Zeno S, Faraday M, Poth M, and Deuster P. Physiologic and Behavioral Correlates of Obesity in African Americans and Caucasians. Presented at the 2006 DoD Military Health Research Forum (MHRF).

8.   Kim SJ, Poth M, Deuster P, Fendrick N, and Zeno S. Differential Hormone Responses to a Liquid Meal and Exercise in African Americans and Caucasians. Presented at The Endocrine Society 2007.

9.   Stephens Q, Deuster P, and Poth M. Applicability of VO2 max Criteria in African American and Caucasian Individuals. Submitted to the American College of Sports Medicine.

10.   Oates CS, Paton JC, Freedman J, Kim SJ, Faraday MM, Deuster PA. Chronic Stress Predicts BMI in African-American Women. American Psychological Association. 2005.

11.   Poth MA, Straight A, Cooper JA, Freedman JA, and Deuster PA. Differences in the Metabolic Response to Stressors as a Function of BMI. Endocrine Society 2005.

12.   Deuster PA, Sutton EE, Paton JC, Faraday M, Straight EE, Sbrocco T, Poth M. Presented at Peer Reviewed Medical Research Program Meeting 2004.

Manuscripts

1.   Kim-Dorner SJ, Poth M, Deuster PA, Remaley AT. Triglycerides and HDL as Surrogates for Insulin Resistance. Submitted to *Metabolism*.

2.   Zeno SA, Kim-Dorner SJ, Deuster PA, Davis JL, Remaley AT, and Poth M. Cardiovascular Fitness and Risk Factors of Healthy African-Americans and Caucasians. Submitted to *Med Sci Sports Exer*.

3.   Zeno SA, Kim-Dorner SJ, Deuster PA, Remaley AT, and Poth M. Ethnic-Specific Criteria for Metabolic Syndrome in African-Americans. Submitted to *Ethnicity & Health*.

4.   Kim-Dorner SJ, Simpson-McKenzie CO, Poth, M, and Deuster PA. Psychological and Physiological Correlates of Insulin Resistance at Fasting and in Response to a Meal in African Americans and Caucasians. In Press. *Ethnicity & Disease*, 19(1).

5.   Kim-Dorner SJ, Simpson-McKenzie CO, Poth, M, and Deuster PA. Stress Coping Style and Insulin Resistance in African-Americans and Caucasians. In Press. *Ethnicity & Disease*: "For the Patient."

Presentations

1.　Frazier, B. Dehydroepiandrosterone and Determinants of Insulin Resistance in African-American Women. Uniformed Services Pediatrics Section March 2009. 2nd Place Winner.

2.　Deuster PA. Risk Factors and Metabolic Syndrome in African-American and Caucasians. Presenting at National Institutes of Health (NIH), Clinical Center's Clinical Pathology Department, Bethesda, MD in October 2008.

2.　Abraham PA, McGill C, Davis J, Zeno SA, C, Deuster PA and Poth M. Physiological Correlates of the Insulin Response to a Test Meal in African American and Caucasian Women. Endocrine Society June 2008.

3.　Kim SJ, Sbrocco T, and Deuster PA. Ethnicity and Insulin Resistance: Role of Chronic Stress, Exercise, and Eating Behaviors. Society of Behavioral Medicine Annual Meeting, San Diego, CA in March 2008.

4.　Deuster PA. "Physiologic and Ethnic Effects on Stress Reactivity" for the Department of Medical and Clinical Psychology on 11 February 2008.

5.　Kim SJ, Poth M, Deuster P, Fendrick N, Zeno S. Differential Hormone Responses to a Liquid Meal and Exercise in African Americans and Caucasians. Endocrine Society June 2007.

6.　Deuster P. "Stress Reactivity: Models, Markers, Meaning, Muddlement" at the Office of Naval Research (ONR) Stress Physiology Program Review Meeting; 25 – 27 July 2007.

7.　Deuster PA. "Exercise as a neuroendocrine stimulus: Exercise responses in health and disease" for the Foundation for Advanced Education in the Sciences Course: Neural Immune Interactions in Health and Disease. April 2007.

8.　Stephens Q. Featured Guest Speaker – Montgomery County Cable Community Comments Television Program (Topic: Cardiovascular Disease and Exercise) in May 2006.

9.　Kim S. HPA Axis Responsivity and Ethnicity. Oral presentation for American Psychological Association meeting in New Orleans, LA in August 2006

10.　Kim SJ, Oates C, Fendrick N, Zeno S, Faraday M, Sbrocco T, Poth M, Deuster P. Physiological and Psychological Correlates of Insulin Resistance in African Americans and Caucasians. Society for Behavioral Medicine 2006.

11.　Fendrick N, Stephens Q, Oates C, Kim S, Zeno S, Faraday M, Poth M, & Deuster P. Physiologic and Behavioral Correlates of Obesity in African Americans and Caucasians. Presented at the 2006 DoD Military Health Research Forum (MHRF).

12.　Stephens Q, Deuster P, and Poth M. Applicability of $VO_{2\,max}$ Criteria in African American and Caucasian Individuals. American College of Sports Medicine May 2007.

13.　Oates CS, Paton JC, Freedman J, Kim SJ, Faraday MM, Deuster PA. Chronic Stress Predicts BMI in African-American Women. American Psychological Association. 2005.

14.　Poth MA, Straight A, Cooper JA, Freedman JA, and Deuster PA. Differences in the Metabolic Response to Stressors as a Function of BMI. Endocrine Society 2005.

15.　Deuster PA, Sutton EE, Paton JC, Faraday M, Straight EE, Sbrocco T, Poth M. Presented at Peer Reviewed Medical Research Program Meeting 2004.

Grants Accepted

1.　P20 NIH USH Health Disparities Research Center

Conclusions

African-Americans (AA) have a higher prevalence and rate of mortality from cardiovascular disease (CVD) than Caucasians (CA) (9-12), the highest age-adjusted prevalence of coronary heart disease (CHD), and higher death rates from stroke than any ethnic group in the United States. Hozawa et al. (5)suggested the higher incidence rate of CVD in AA may be largely attributable to a higher prevalence of risk factors and postulated that awareness of these risk factors might help eliminate the health disparity in CVD incidence.

Mosca et al. (16) showed that awareness of CVD as the leading cause of death was independently correlated with increased physical activity and weight loss in the previous year among women, and suggested that awareness of CVD may be important for primary prevention. Interestingly, Christian et al. (2) reported that awareness of CVD risk factors was significantly lower for AA and Hispanic women than CA women. Together these data suggest that awareness of elevated CVD risk factors in AA might lead to effective primary prevention and thus greatly reduce CVD occurrence, as it has in CA (16).

One strong predictor of all-cause and CVD mortality is cardiovascular fitness (1, 3, 6, 19, 23, 24). The strong inverse relationship between CVD death and cardiovascular fitness categories recently prompted Steven Blair (1) to suggest that physical inactivity may be one of the most important public health problems of the 21st century. Improvements in fitness correspond to reductions in blood pressure (19, 23), improvements in insulin sensitivity (3), and lower levels of C-reactive protein (CRP) (8), and regular physical activity and exercise have independent actions for reducing the risk of CVD (1, 4, 23, 32). Even a modest increase in aerobic fitness level has been shown to have a significant impact on insulin sensitivity, lipoprotein parameters and overall risks for CVD in sedentary overweight or obese African-American women (3, 13-15, 17, 18).

Insulin resistance is also more common in AA than CA, and this may in part be explained by heightened sensitivity to glucocorticoids and stress (4, 7, 20, 25, 29). We have shown through our work that AA also have heightened insulin release compared to CA in response to the same meal. However, waist circumference was not a good surrogate for insulin resistance in AA. Moreover, cardiovascular fitness was low in AA relative to CA and highly related to both insulin levels and percent body fat. Importantly, triglycerides and HDL were unrelated to fasting insulin in AA but related in CA (11). Thus ethnic specific criteria need to be use to assess risk for the diseases for which AA are most susceptible. Our data have yielded many important findings, and will hopefully change the way risk for disease is approached.

We successfully met our goals for the final year of the study: completion of testing participants, analyzing data, completing biochemical and statistical analyses, and examining data for HPA reactivity, resistance to feedback control and insulin resistance, and exercise-associated increases in insulin and glucocorticoid sensitivity. We examined differences between CA and AA in terms of potential underlying causes of metabolic syndrome and how different physiologic stressors activate the HPA axis. Importantly, we related and explored metabolic processes intrinsic to obesity and associated CHD risk factors as a function of ethnicity. This has also been suggested by others (21-24, 26-28, 30-33). We expect to add to the body of knowledge that surrounds metabolic syndrome, because of our comparative design with factors of ethnicity, weight, and gender.

Over the past five years, we achieved all goals for this project. Notably, we enrolled 160 participants and completed testing on 126 participants. In addition, nine abstracts were submitted and we gave several presentations based on our physiological, biochemical, and psychological testing. We have prepared five manuscripts on the following topics: stress coping style and insulin resistance; psychological and physiological correlates of insulin resistance at fasting and response to a meal in AA and CA; ethnic-specific criteria for metabolic syndrome in AA; cardiorespiratory risk factors for AA and CA; and, triglycerides and HDL as surrogates for Insulin Resistance. Two of the five manuscripts were published and three are in consideration. Several more will be prepared over the next year.

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APPENDICES

1.   Kim-Dorner SJ, Simpson-McKenzie CO, Poth, M, and Deuster PA. Psychological and Physiological Correlates of Insulin Resistance at Fasting and in Response to a Meal in African Americans and Caucasians. In Press. *Ethnicity & Disease*, 19(1).

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PSYCHOLOGICAL AND PHYSIOLOGICAL CORRELATES OF INSULIN RESISTANCE AT FASTING AND IN RESPONSE TO A MEAL IN AFRICAN AMERICANS AND WHITES

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Background: African Americans are more insulin resistant than are Whites. The purpose of this study was to characterize physiologic and psychological (stress coping style) correlates of insulin resistance in African Americans and Whites.

Methods: We examined African American (*n* = 67) and White (*n* = 41) men and women aged 18–45 years with body mass index 18–35 kg/m^2. We used the homeostasis model assessment (HOMA-IR) and area under the curve for insulin (AUC) after a standardized meal as measure of insulin resistance. We obtained anthropometric measures and determined maximal aerobic power (VO$_{2max}$) by treadmill exercise. We used stress profile to assess stress and coping style.

Results: Postprandial insulin AUCs were higher in African Americans than in Whites. Anthropometric measures and VO$_{2max}$ were related to HOMA-IR and AUC. Although self-reported stress level did not differ between Whites and African Americans, positive appraisal predicted reduced HOMA-IR and negative appraisal coping style predicted increased insulin AUC.

Conclusions: Psychosocial factors may be determinants of health and targets of intervention for obesity-related disorders such as insulin resistance. Existing behavioral intervention programs, designed with a sole emphasis on exercise and nutrition, may fall short of optimal effectiveness. (*Ethn Dis.* 2009;19:104–110)

Key Words: Insulin Resistance, Stress, Ethnicity, Coping Style

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INTRODUCTION

Insulin resistance, characterized by a relative lack of physiologic responsiveness to insulin, is a common biological marker for the early identification of type 2 diabetes mellitus.[1] Insulin resistance is more prevalent in obese than healthy weight people,[2,3] and fasting and stimulated insulin and glucose concentrations are higher in obese people as a group, compared with healthy weight controls.[4] In addition, African Americans are more insulin resistant than are Whites.[5–8] High prevalences of insulin resistance in African Americans may parallel obesity in African Americans because excessive body fat is considered the single most important risk factor for insulin resistance and diabetes.[9–12] However, at each body mass index (BMI) category, the glucose and insulin responses of African Americans resemble the metabolic profile of more obese people.[13] Such evidence suggests that African Americans may be more prone to developing metabolic profiles associated with obesity, insulin resistance, and diabetes.

Interethnic differences in the prevalence of insulin resistance may reflect genetic differences, such as genetically determined metabolic differences,[14] but they may also result from environmental exposures. One possible cause for the differential prevalence in insulin resistance between Whites and African Americans may be the experience of and response to chronic stress. African Americans report high levels of chronic stress from factors that disproportionately affect them, including unemployment, low socioeconomic status, limited healthcare access, and racial discrimination.[15] These factors are associated with negative effects on psychological and physical well-being.[16] For example, the release of glucocorticoids during periods of chronic stress increases plasma glucose; this pattern has been associated with decreased insulin sensitivity.[17,18] The appraisal of stress and subsequent coping responses in specific ethnic populations[19] may further contribute to potential disease states, such as diabetes and other metabolic disorders.

The high prevalence of insulin resistance, obesity, and diabetes in African Americans demonstrates the need to understand the psychological correlates of insulin resistance in this specific high-risk group. The purpose of the current study was to examine the relationships between psychological variables and insulin resistance in an effort to explain the development of metabolic dysregulation. Specifically, we sought to characterize psychological correlates of insulin resistance with an emphasis on the role of psychological stress and cognitive coping styles and the relationship between insulin resistance and physiologic and anthropometric variables in African Americans and Whites.

> *The purpose of the current study was to examine the relationships between psychological variables and insulin resistance in an effort to explain the development of metabolic dysregulation.*

METHODS

Participants

Self-identified African American and White men and women aged 18–45 years who had BMI values 18–35 kg/m² were recruited via local newspapers and from local universities in the Washington DC metropolitan area. Participants were healthy and medication-free at the time of participation. Participants with one or more of the following conditions were excluded from the study: 1) pregnancy, menopause, diabetes, liver and pancreatic diseases; 2) heart disease; 3) fasting blood glucose ≥125 mg/dL and blood pressure >140/90 mm Hg; and 4) active suicidal ideation. The study was approved by the institutional review board of the Uniformed Services University of the Health Sciences, and written informed consent was obtained from all participants.

Laboratory Visit

Qualified participants visited the laboratory between 7 and 8 a.m. All participants were required to abstain from caffeine, alcohol, tobacco, and strenuous exercise for at least 12 hours before the laboratory visit. An indwelling catheter was placed in the antecubital vein of a forearm; the catheter line was kept open with a heparin lock.

Next, the participants drank 5 mL/kg of their body weight in water to ensure adequate hydration before exercise. Approximately 40 minutes were allowed for absorption of the water. During this period, the stress profile was administered. After this 40-minute period, participants drank 2 cans of Ensure-Plus as their breakfast meal. A 5-minute period was allotted for the liquid meal ingestion. Approximately 2 hours after ingesting the standardized meal, participants underwent a maximal exercise treadmill test to determine maximal aerobic power. Before the maximal aerobic power test, a medical history, physical examination, and resting 12-lead electrocardiogram were

carefully examined by a physician for the participant safety.

Measures

Body weight was measured with a calibrated balance beam metric scale to the nearest 0.1 kg, and height was measured to the nearest 0.1 cm while the participant was wearing light clothing and no shoes. BMI was calculated from height and weight. Percentage body fat was estimated by bioelectric impedance with the portable RJL body composition analyzer (RJL Systems). Waist circumferences were measured with an inelastic tape around the waist and hip by using standard techniques.[20]

The stress profile[21] has 123 items that provide scores in multiple areas related to perceived stress and health risk. Conceptually, the stress profile is based on the framework of stress and coping.[19] Internal consistency is satisfactory ($r = .72$) and reliability is adequate ($r = .76–.86$) and has been validated on an ethnically diverse population.[21] The Cronbach α for our sample was .82. Selected subscales used for this study are described below.

The stress subscale (6 items) addressed perceived stress experienced in the last 3 months. Stress is defined as the experience of major and minor irritants, annoyances, and frustrations of daily living such as health, work, financial, family, social, and environmental hassles. Participants are asked how frequently they experience stress in these areas by using a 5-point Likert scale ranging from never to always.

The social support network subscale contains 15 items assessing emotional support, assistance on a regular basis, use of support, and the satisfaction of the support that the respondent receives from the immediate environment.

The stress profile also includes cognitive coping strategy items. The coping style subscales consist of 4 areas (positive appraisal, negative appraisal, threat minimization, and problem-focus) that address specific coping strategies. Coping

style is the most common way that people deal with work and life stress. Positive appraisal (5 items) is characterized by employing supportive and encouraging self-talk to cope with a challenging situation. People who employ positive appraisal can often generate favorable outcomes. Negative appraisal (5 items) is the tendency to approach a difficult life situation with self-blame, criticism, or catastrophic thinking. This coping strategy focuses on the worst possible outcome. Threat minimization (5 items), also referred to as avoidance, is a coping strategy that emphasizes the humor in problematic situations and often distracts attention from the stressor. Problem focus (4 items) is the degree to which a person devises a specific course of action for reducing the effect of current problems. This coping style emphasizes the tendency of trying to improve the troublesome situation.

Changes in plasma glucose and insulin were monitored at baseline and 10, 30, 50, and 70 minutes after participants drank 16 oz Ensure-Plus (720 kcal, 56.4% carbohydrates, 29% fat, and 14.6% protein). This liquid meal has been used to stimulate both glucose and insulin responses.[22,23]

Each participant completed a progressive maximal exercise test to determine maximal aerobic power (VO_{2max}). The exercise test was carried out on a treadmill (Quinton ST-65, Quinton Instrument Company, Seattle, Wash) and involved a 5-minute warm-up (3.0 mph, 2% grade) followed by walking (or running) at 2.5–7.0 mph (depending on heart rate during the warm-up), as grade increased by 2.5% every 2 minutes until the subject reached volitional exhaustion. Participants were instrumented with electrodes (Quinton Q-4500) and a portable metabolic unit for continuous monitoring of heart rate and electrocardiogram, and oxygen uptake, carbon dioxide production, and respiratory exchange ratio by open-circuit spirometry (KB20-CosMed, Rome, Italy). A 5-minute

cool-down (2.5 mph, 0% grade) followed the maximal exercise testing. Verification that each volunteer actually achieved maximum VO_{2max} criteria was determined by plateau of VO_{2max} or meeting at least 3 of the following 4 criteria: respiratory exchange ratio ≥ 1.1, age-predicted maximal heart rate, a score ≥ 17 on the Borg perceived exertion scale rating, or a blood lactate value ≥ 8 mmol/L. Spotters and trained medical personnel were present during the exercise test.

Blood for hormones was collected in EDTA, immediately placed on ice, and then centrifuged within 30 minutes of collection. Insulin levels were measured by standard radioimmunoassay (Diagnostic Systems Laboratories Incorporated, Webster, Texas). All plasma was stored at $-70°C$ and assayed in duplicate and in batch to minimize interassay variability. Intraassay and interassay coefficients of variation were <10%.

Statistical Analysis

Fasting IR was calculated by the homeostasis model assessment method of insulin resistance (HOMA-IR)[24] by using morning fasting plasma insulin and glucose samples. The area under the curve (AUC)[25] for insulin was used for a stimulated insulin resistance measure. Fasting insulin, HOMA-IR, insulin peak, and AUC were natural log transformed.

Independent t tests and χ^2 analyses were used to examine the participant characteristics and baseline measures. Multivariate analyses of variance were used to examine the anthropometric measures and stress profile data between African American and White partcipants. Postprandial metabolic measures were examined by using repeated measures of analysis of variance, and fasting and summarized postprandial glucose and insulin measures were analyzed by using multivariate analysis of variance. Relationships among insulin resistance, anthropometric and psychological measures, and VO_{2max} were examined by

using the correlations and hierarchical linear regressions. All data analyses were conducted by using SPSS version 15.0 (SPSS Inc, Chicago, Ill). Differences were considered significant at P < .05.

RESULTS

Demographics and Baseline Physiologic Measures

Of the 160 participants who visited the laboratory for the original study, 11 were excluded for not meeting the inclusion criteria. After excluding 41 more people with missing or incomplete data, a total of 108 participants were included in the study. White and African American participants were comparable in sex, education, income, and anthropometric measures, but African Americans were older and had significantly lower cardiorespiratory fitness levels than did Whites (Table 1). VO_{2max} remained significantly lower for African Americans even after accounting for age difference and BMI, P = .005. Eight Whites (20%) and 12 African Americans (18%) were smokers.

Metabolic Measures

There was no difference in fasting glucose concentrations between African Americans and Whites, but African Americans had higher fasting insulin concentrations, P = .014, and higher HOMA-IR values, P = .03 (Table 1). However, after adjusting for age and VO_{2max}, fasting insulin and HOMA-IR did not differ between the ethnic groups. Sex did not make a difference in fasting insulin or the HOMA-IR.

Figure 1 shows the plasma concentrations of insulin for a 70-minute period after a meal. African Americans and Whites did not differ in plasma glucose in response to a meal, but insulin response was higher in African Americans than in Whites, P < .001. African Americans had higher insulin concentrations even after accounting for the age and VO_{2max} difference, P =

.013. The higher postprandial insulin concentrations in African Americans was further confirmed in total insulin AUC, P < .001 (Table 1). The difference remained even after accounting for age and VO_{2max}, P = .014. Glucose AUC did not differ by ethnicity.

Stress and Coping Strategies

African Americans did not report higher level of stress than did Whites. However, African Americans reported more frequent use of positive appraisal as a coping mechanism than did Whites, P = .003. African Americans and Whites did not differ on social support (trend P = .066), negative appraisal, threat minimization, and problem-focused coping.

Stress, Coping Style, Anthropometric Measures, and Insulin Resistance

Correlational analyses revealed significant associations among anthropometric measures, P < .001, and all anthropometric measures were positively correlated with HOMA-IR and insulin AUC (Table 2). Increased anthropometric measures were related to reduced VO_{2max} as well as increased HOMA-IR and insulin AUC. African Americans and Whites had similar patterns.

Increased stress was associated with increased BMI, percentage body fat, and postprandial insulin AUC. Increased stress was associated with reduced VO_{2max}. Increased social support was related to reduced abdominal obesity, and positive appraisal was related to reduced BMI and HOMA-IR. Negative appraisal was only related to increased insulin AUC.

The role of stress and coping strategies for HOMA-IR and insulin AUC were examined by using a hierarchical regression analysis (Table 3). The contributions on HOMA-IR and insulin AUC were examined along with demographic and physiologic variables.

Table 1. Demographic, anthropometric, and metabolic characteristics of 108 White and African American participants

Variable	*n* or mean (SD)	
	White (*n* = 41)	African American (*n* = 67)
Demographic characteristics		
Age, years*	28.2 (5.3)	31.3 (8.3)
Sex (women/men)	18/23	32/35
Education		
Less than high school	0	1
High school	0	3
Some college	16	33
College graduate	25	30
Annual Income, $		
<25,000	5	20
25,000–50,000	15	28
50,001–80,000	11	12
>80,000	6	5
Missing data	4	2
Anthropometric measures		
BMI (kg/m^2)	26.6 (4.5)	26.8 (3.9)
BMI category (healthy weight/overweight/obese)	15/15/11	22/28/17
Waist circumference (cm)	86.0 (14.3)	85.5 (11.2)
Body fat (%)	28.8 (8.7)	30.5 (7.7)
VO$_{2max}$ (mL/kg/min)†	43.9 (9.1)	37.0 (10.0)
Metabolic measures		
Fasting glucose (mmol/L)	5.2 (.62)	5.1 (.70)
Fasting insulin (μIU/mL)	8.7 (5.78)	11.4 (6.60)
Ln fasting insulin*	2.0 (.55)	2.3 (.56)
HOMA	2.0 (1.33)	2.7 (1.75)
Ln HOMA*	.54 (.56)	.80 (.60)
Glucose peak (mmol/L)	6.6 (.98)	6.7 (1.48)
Glucose AUC (mmol/L•80 min)	456.7 (60.81)	456.7 (101.51)
Insulin peak (μIU/mL)	121.4(99.77)	193.29 (150.41)
Ln insulin peak†	4.5 (.72)	5.0 (.70)
Insulin AUC (μIU/mL•80 min)	5068.9(3670.2)	8513.9 (6453.1)
Ln insulin AUC‡	8.3 (.62)	8.8 (.69)

SD = standard deviation, BMI = body mass index, VO$_{2max}$ = maximum oxygen consumption, HOMA = homeostasis model assessment of insulin resistance, AUC = area under the curve.

* $P < .05$.
† $P < .01$.
‡ $P < .001$.

These predictor factors were entered in 4 separate models.

The overall model accounted for 38% of the variance of HOMA-IR, and the model was significant, $R^2 = .384$, P $< .001$. In this model, sex, VO$_{2max}$, and positive appraisal were significant predictors of HOMA-IR. Men had higher HOMA-IR, and higher cardiovascular fitness reduced HOMA-IR. Positive appraisal of stress reduced HOMA-IR, and ethnicity was not a contributor in HOMA-IR.

The overall model for insulin AUC was significant, $R^2 = .528$, P $< .001$.

Higher fasting insulin concentrations predicted higher postprandial insulin concentrations. Furthermore, ethnicity (being African American) significantly contributed to higher postprandial insulin response, and negative appraisal of stress also predicted higher insulin AUC.

DISCUSSION

The present study examined physiologic and psychological correlates of fasting and stimulated insulin resistance in African American and White men

and women. Insulin AUCs in response to a meal were significantly higher in African Americans than in Whites, and this hyperinsulinimic postprandial response in African Americans could not be completely explained by any one or combination of baseline characteristics (eg, age, sex, anthropometric measures, VO$_{2max}$). This finding was interesting considering African Americans and Whites had comparable plasma glucose concentrations at all times. This study confirmed that African Americans may require more insulin to remove the same amount of glucose from the bloodstream
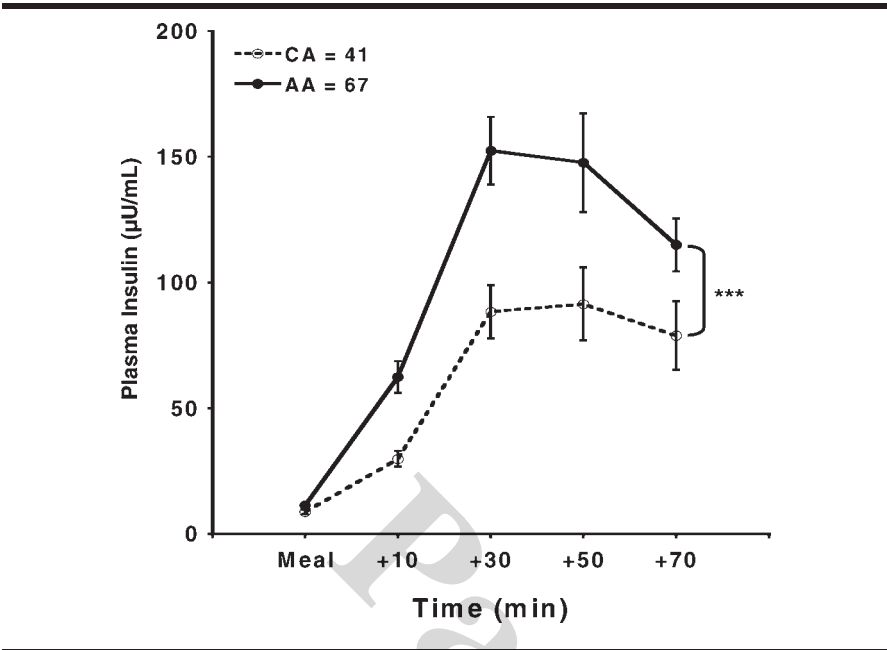
Fig 1. Postprandial insulin concentrations after a meal by ethnicity. ***$P < .001$.

This study confirmed that African Americans may require more insulin to remove the same amount of glucose from the bloodstream than do Whites.[6]

than do Whites.[6] Hyperinsulinemia is associated with obesity; however, in this study, even after accounting for age, BMI, and cardiovascular fitness, African Americans released more insulin than did Whites after a meal.

Of particular note was the finding that cardiovascular fitness (VO_{2max}) was significantly higher in Whites than in African Americans, regardless of their age. Moreover, VO_{2max} was negatively correlated with both fasting and stimulated insulin resistance and all anthropometric measures. In the regression, VO_{2max} was the only significant physiologic predictor for HOMA-IR.

Psychological and behavioral variables contribute to the development of insulin resistance differently in African Americans as compared with Whites. Previous studies reported high levels of chronic stress in African Americans from factors that are disproportionately common in African Americans, such as low socioeconomic status. This difference in socioeconomic status may serve as a daily stressor in African Americans. However, in the current study, overall self-reported chronic stress did not differ by group. Comparable levels of stress between Whites and African Americans may be in part explained by comparable socioeconomic status of the 2 groups. In this study, almost all participants had received at least a partial college education, and the annual income was comparable between African Americans and Whites. Interestingly, when the financial hassle item from the stress subscale was

Table 2. Correlation of HOMA and insulin AUC with anthropometric and stress measures and VO_{2max}

	BMI	Waist	Body fat	VO_{2max}	Stress	Social Support	Positive Appraisal	Negative Appraisal	Threat Minimization	Problem Focus	LnHOMA
BMI	1										
Waist	.84*	1									
Body fat	.60*	.39*	1								
VO_{2max}	−.50*	−.38*	−.75*	1							
Stress	.24†	.12	.25‡	−.22†	1						
Social Support	−.19	−.25‡	−.09	.13	−.19	1					
Positive Appraisal	−.21†	−.13	−.14	.03	−.22†	.22†	1				
Negative Appraisal	.19	.08	.13	−.02	.52*	−.19†	−.25‡	1			
Threat Minimization	.04	.11	−.03	.04	−.03	.25‡	.50*	−.05	1		
Problem Focus	−.13	−.05	−.02	.14	−.09	.27‡	.44*	−.20†	.52*	1	
LnHOMA	.44*	.43*	.32‡	−.48*	.13	−.11	−.20†	.07	−.06	−.19	1
Ln In AUC	.29‡	.30‡	.27‡	−.43*	.21†	−.01	−.08	.23†	.01	−.09	.66*

HOMA = homeostasis model assessment of insulin resistance, AUC = area under the curve, VO_{2max} = maximum oxygen consumption, BMI = body mass index.
* $P < .001$.
† $P < .05$.
‡ $P < .01$.

Table 3. Hierarchical multiple linear regression analysis

LN HOMA-IR	R	R² Change	β	LN Insulin AUC	R	R² Change	β
Sex (male)	.158	.025	.057	Sex (male)	.119‡	.014	.088
Age			.153	Age			−.073
Sex (male)	.593‡		.257†	Sex (male)	.475‡		−.169
Age			−.170	Age			.119
BMI		.326***	.212*	BMI		.212‡	.091
VO₂max			−.564‡	VO₂max			−.518I
Sex (male)	.597‡		.241*	Sex (male)	.700‡		−.090
Age			−.177	Age			−.043
BMI			.232*	BMI			.031
VO₂max			−.526‡	VO₂max			−.101
Ethnicity (AA)		.005	.075	Ethnicity (AA)		.264‡	.182*
				Fasting insulin			.573I
Sex (male)	.620‡		.258*	Sex (male)	.726‡		−.056
Age			−.146	Age			.032
BMI			.196	BMI			−.026
VO₂max			−.521‡	VO₂max			−.167
Ethnicity (AA)			.139	Ethnicity(AA)			.176*
				Fasting Insulin			.554I
Stress		.028	−.007	Stress		.038	.022
Social support			.076	Social Support			.129
Positive appraisal			−.187*	Positive Appraisal			−.007
Negative appraisal			.005	Negative Appraisal			.178*

Note: * $P < .05$; † $P < .01$; ‡ $P < .01$.

examined alone, African Americans reported more frequent financial hassles than did Whites, P = .003.

African Americans also reported more positive appraisal than did Whites, and positive appraisal had influence on reducing HOMA-IR. Cognitive appraisal mediates responses to stress.[19] Situations that threaten physical or psychological well-being can be appraised as either positive or negative. Positive appraisal minimizes the stressor by resulting in an optimistic perspective about the situation; in contrast, negative appraisal is defined by a reliance on catastrophic thinking.[21] Catastrophic thinking adversely affects mood states and is more likely to exacerbate the stress response.[19] Previous research has suggested that maladaptive (passive or negative) coping strategies are associated with an increased health risk.[26–28] In our study, negative appraisal reduced increased insulin AUC after a meal.

The current investigation has several weaknesses. First, perceived racial and ethnic discrimination or racism-specific coping responses were not directly measured in this study. The environmental hassle included stress associated with prejudice, but no language was used to address race-related prejudice or associated stress. It may be important to quantify these episodes of racism in order to understand their effect on mental and physical health outcomes. Second, our study included healthy people of BMI 18–35 kg/m². The negative effect of stress may be more pronounced in severely obese people or those with health problems. However, because of the physical demand of VO₂max exercise protocol and to safeguard our participants against any injury, we used only healthy participants. Generalizability of the findings may be limited to relatively healthy people with BMI <35 kg/m².

In summary, in addition to cardiovascular fitness, the significant associations between psychological factors and insulin resistance among participants implies that stress and adaptive coping mechanisms, such as positive appraisal, may be indicators of health risks and targets of intervention for obesity-related disorders, to include insulin resistance. The implication from this study is that existing behavioral intervention programs with a sole emphasis on exercise and nutrition may fall short of optimal effectiveness in targeting groups at high risk for insulin resistance and obesity. Positive coping strategies seem to be complements to a well-managed exercise and nutrition program to reduce the risk of insulin resistance in both African Americans and Whites, on the basis of this particular sample. Future studies are warranted to determine whether these findings are applicable to other ethnic minorities - particularly those at risk for metabolic disorders, such as some Latino and Native American subgroups.

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Short Title: Stress Coping Style and Insulin Resistance

in African Americans and Caucasians

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An early indication of developing diabetes is insulin resistance, characterized by the body's inability to respond to "normal" insulin levels. Insulin resistance is more common in obese than normal weight individuals, and in African Americans than Caucasians. However, even after matching for obesity status, African Americans remain more insulin resistant than Caucasians. This racial difference in the insulin resistance may reflect biological differences between these two ethnic groups, but it may also result from environmental exposures. One other possibility is chronic stress, since stress can interfere with insulin actions and African Americans are reported to experience more chronic stress than Caucasians.

In our study, we have examined how physiological factors and the experience of and response to chronic stress affect insulin resistance in young, healthy African Americans and Caucasians. We found that African Americans and Caucasians had comparable blood sugar levels after eating the same meal, but blood insulin levels were much higher in African Americans compared to Caucasians. This indicates over-production of insulin by the pancreas in African Americans relative to Caucasians. In other words, the body is not effectively responding to insulin's action, which is to lower the blood sugar level.

We also found that low physical fitness contributed to being .insulin resistant, regardless of ethnicity. When stress levels and stress responses were examined, African Americans did not report more chronic stress than Caucasians, but African Americans reported using a stress coping strategy called "positive appraisal" more frequently than Caucasians. Positive appraisal is characterized by using supportive and encouraging self-talk to cope with a challenging situation. Individuals who use positive appraisal are often able to generate favorable outcomes. In our study, this positive appraisal coping mechanism predicted less insulin resistance. Also, negative appraisal, which is the

opposite of positive appraisal and characterized by self-blame, criticism, or catastrophic thinking, was associated with greater insulin resistance.

These coping strategies, positive or negative appraisal, serve to modify individual responses to stress. Situations that threaten physical or psychological well-being can be appraised or judged as either positive or negative. Positive appraisal minimizes the stressor to create an optimistic perspective about the situation; in contrast, negative appraisal may exaggerate the stressor to adversely affect mood states and is more likely to exacerbate the stress response. In our study, negative appraisal was associated with increased insulin resistance and positive appraisal reduced insulin resistance. This shows how important coping strategies and other behaviors may be in affecting insulin resistance.

There is no cure for diabetes. Early identification and treatment of insulin resistance to prevent the progression to diabetes is the best treatment available. Our study shows that adaptive stress coping strategies, such as positive appraisal, may be important complements to a well-managed exercise and nutrition program for reducing insulin resistance and its related negative health outcomes, such as diabetes. Existing intervention programs that only emphasize exercise and nutrition may fall short of optimal effectiveness in reducing insulin resistance.

SHOULD TRIGLYCERIDES AND THE TRIGLYCERIDES TO HDL-C RATIO BE USED AS SURROGATES FOR INSULIN RESISTANCE?

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DISCLAIMER:

The opinions and assertions expressed herein are those of the authors and should not be construed as reflecting those of the Uniformed Services University of the Health Sciences (USUHS) or the Department of Defense.

INSTITUTIONAL APPROVAL:

The study was conducted at the Uniformed Services University of the Health Sciences (USUHS), Bethesda, Maryland, USA. The authors and researchers involved in this study complied with ethical standards in the treatment of the human subjects in this study, and are in compliance with regulations of the USUHS Institutional Review Board. All participants went through the informed consent procedure, knew risks and benefits associated with participation in the study, and provided written consent prior to participation. This study was approved and monitored by the Uniformed Services University of the Health Sciences Institutional Review Board.

CONFLICT OF INTEREST:

All authors declare that there is no conflict of interest.

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ABSTRACT

The aims of the present study were to examine the relationship between lipid profiles and insulin resistance in African Americans and Caucasians. This cross-sectional study included 99 African American and 50 Caucasian men and women between 18-45 years of age with body mass indexes between 18-38 kg/m2. Anthropometric measures were obtained and overnight fasting blood was collected for triglycerides (TG), high density lipoprotein cholesterol (HDL-C), glucose and insulin. Insulin resistance was defined by fasting insulin concentration ≥ 13.13 μIU/mL and HOMA-IR ≥ 2.5. The triglyceride to HLD cholesterol ratio was calculated as TG/HDL-C. Receiver operating characteristic (ROC) curves were used to analyze the data. African Americans and Caucasians had comparable demographic and anthropometric measures. Although fasting insulin and HOMA-IR appeared higher in African Americas, the difference was not statistically significant: TG and TG/HDL-C were significantly higher in Caucasians. Both TG and TG/HDL-C were acceptable markers for insulin resistance measured as HOMA-IR in Caucasians; area under the ROC curves were 0.763 and 0.770, respectively. However, TG and TG/HDL-C were poor predictor of HOMA-IR in African Americans, 0.625 and 0.639, respectively. Similarly, areas under the ROC curves showed that TG and TG/HDL-C were acceptable in predicting insulin resistance as defined by fasting insulin concentration in Caucasians, 0.770 and 0.765, respectively, whereas the predictability was poor for African Americans, 0.633 and 0.651, respectively. In conclusion, the relationship between lipids and insulin resistance differs by ethnicity, and using lipid measures to predict insulin resistance or metabolic syndrome in African Americans would not be appropriate.

INTRODUCTION

Insulin resistance, characterized by an inadequate physiological response to insulin, is one of the major risk factors for type 2 diabetes mellitus (T2DM) (1, 2). When impaired glucose metabolism is actually detected by elevated fasting glucose concentrations or a glucose tolerance test, a significant proportion of β-cells may have already been destroyed or compromised (3). There is no cure for diabetes; thus, preventing is the best interventions. However, if insulin resistance is detected early, while glucose responses are still intact, interventions are more likely to be successful.

It is well established that insulin resistance is associated with cardiovascular disease (CVD) development and death (4-6). Therefore, the aggregation of CVD risk factors, or metabolic syndrome, has been developed to identify individuals at an increased risk for CVD, with insulin resistance as the common denominator that precedes other facets of the syndrome (6, 7). However, the use of insulin resistance as one of the criteria for metabolic syndrome was limited by the impracticality of quantifying insulin resistance in clinical settings. Thus, surrogates of insulin resistance, which would be more practical and reliable in clinical settings, were proposed.

Triglycerides (TG) and the triglyceride to high-density lipoprotein cholesterol (HDL-C) concentration ratio (TG/HDL-C) have been reported to be closely related to insulin resistance, and use of TG and TG/HDL-C as surrogates for insulin resistance has been recommended (8-10). On the other hand, some authors have emphasized inter-ethnic differences in lipid profiles and insulin resistance, and cautioned the use of lipid surrogates for insulin resistance. In fact, recent literature show that African Americans (AA) have more favorable lipid profiles than Caucasians (CA) despite AA being more

insulin resistant (11-13). Therefore, the aim of our study was to examine how well insulin resistance could be predicted in a group of young healthy AA and CA participants using TG and TG/HDL-C.

METHODS

Participants

AA and CA men and women between the ages of 18-45 years were recruited from the surrounding Washington DC metropolitan area. Of the 160 volunteers, data for 99 AA (45 males; 54 females) and 50 CA participants (26 males; 24 females) were available for analysis. Participants were free of other known major diseases, such as heart disease, diabetes, peripheral vascular disease, liver disease, thyroid and other endocrine diseases, or on medication for any of these conditions. Each volunteer underwent a thorough telephone health screening and an on-site medical examination to ensure that all inclusion/exclusion criteria were met. Participants' body mass index (BMI) values ranged between 18-38 kg/m^2, and participants were recruited by BMI category to achieve a comparable distribution among normal weight, overweight, and obese participants.

All participants were informed of the purposes and procedures of the study and provided written consent prior to participation. This study was approved and monitored by the Uniformed Services University of the Health Sciences Institutional Review Board.

Procedures/Measurements

Participants reported to the laboratory at the university between 7 and 8 am after overnight fast. Participant assessments included anthropometric measures (weight,

height, waist and hip circumferences, and percent body fat), and blood draws for fasting blood glucose, insulin, and lipid profiles (total cholesterol, TG, HDL-C, and calculated LDL-C).

Body weight was measured with a calibrated balance beam metric scale to the nearest 0.1kg, and height was measured to the nearest 0.1cm while the participant was wearing light clothing and no shoes. BMI was calculated by weight in kg divided by height in meters squared. Percent body fat was estimated by bioelectric impedance with the portable RJL body composition analyzer (RJL Systems, 1992) by using the NHANES formula (14). Waist circumference was measured with an inelastic tape around the waist by standard techniques (15).

Blood was collected in fasting state by standardized venipuncture techniques between 8 and 9 am. Samples were collected with anticoagulant for insulin and lipid profiles, and in sodium fluoride tubes for glucose. Plasma was extracted and stored in a -80˚C freezer. Blood glucose concentration was measured with the YSI Biochemistry Analyzer Model 2700/115V (Yellow Springs Instrument Co., Inc., Yellow Springs, OH). Serum insulin was measured by standard radioimmunoassay (Diagnostic Systems Laboratory-1600; Webster, TX). Insulin samples were assayed in duplicate and samples with an insulin concentration greater than 200 μIU/mL were diluted and re-tested. Intra- and inter-assay coefficients of variation were <10%. All samples were within 0.2 μIU/mL apart or a third sample was measured; the closest two measurements were used. Lipid profiles were determined at the National Institutes of Health Department of Laboratory Medicine using a LX-20 analyzer (Beckman, San Diego, CA). LDL-C was calculated by the Friedewald equation.

Definition of Insulin Resistance

Insulin resistance was defined using the 75th percentile cutoff values of the fasting insulin concentrations among non-diabetic participants in the National Health and Nutrition Examination Survey (NHANES) 1999-2002 data (9, 16). The 75th percentile cutoff was 13.13 µIU/mL. Insulin resistance was also defined by using the homeostasis model assessment method of insulin resistance (HOMA-IR) [(glucose (mmol/L) x insulin (µIU/mL)/22.5] values ≥ 2.5 (17).

Statistical Analyses

Data are presented as mean ± standard deviation. Chi-squared analyses and MANOVAs were used to compare baseline characteristics by ethnicity. For MANOVA, parameters were transformed if they were not normally distributed, and analyses were only performed using transformed data. However, untransformed data are presented in the table. Areas under the receiver operating characteristic (ROC) curves were used to examine the predictive value of TG and the TG/HDL-C for insulin resistance measures in CA and AA. The areas under the ROC curves are presented with standard errors. The statistical significance level was set at < 0.05, and all data were analyzed using the SPSS statistical package (SPSS, version 16.0.1; SPSS, Inc., Chicago, IL).

RESULTS

The demographic information of 99 AA and 50 CA participants are presented in Table 1. AA were slightly older than CA, but AA and CA did not differ by % of female, education and income, and anthropometric measures. Fasting morning glucose, HOMA-IR, blood pressure, total cholesterol, and LDL-C did not differ by ethnicity; but fasting

insulin concentrations and HDL-C were significantly higher and TG and TG/HDL-C ratio were significantly lower in AA compared to CA.

When fasting insulin concentration was applied to the definition of insulin resistance,13 (26%) of CA and 35 (35.4%) of AA were found to be insulin resistant. Using the HOMA-IR cutoff method, 17 (34%) of CA and 45 (45.5%) of AA were classified as insulin resistant. When the TG and the TG/HDL-C cutoffs recommended for predicting insulin resistance in a previous study were used (TG ≥ 130 and TG/HDL-C ≥ 3) (10), we found that 13 (26%) CA and 9 (9.1%) AA fell into the high TG category and 17 (34%) CA and 12 (12.1%) AA were in the high TG/HDL-C category. The proportion of CA and AA with meeting TG and TG/HDL-C cutoffs differed significantly between the two ethnic groups, $\chi2$ (1, N = 149) = 7.55, p = .006 and $\chi2$ (1, N = 149) = 10.15, p < .001, respectively.

Figure 1 shows the ROC curves predicting insulin resistance using TG and TG/HDL-C in CA and AA. The area under the ROC curves for potential markers of insulin resistance are presented in Table 2 by ethnicity. Figure 1A and B show the ROC curve predicting HOMA-IR using TG and TG/HDL-C for CA and AA, respectively. Both TG and TG/HDL-C were acceptable markers for insulin resistance as estimated by HOMA-IR in CA: 0.763 ± .074 and 0.770 ± .084, respectively. In contrast, both TG and TG/HDL-C were poor predictors for HOMA-IR in AA: 0.625 ± .056 and 0.639 ± .055, respectively. Similarly, areas under the ROC curve showed that TG and TG/HDL-C were acceptable in predicting insulin resistance as defined by fasting insulin concentration in CA: 0.770 ± .084 and 0.765 ± .083, respectively; whereas the predictability remained poor for AA: 0.633 ± .056 and 0.651 ± .055, respectively (Figure

1C & D).

The best surrogate of both HOMA-IR and fasting insulin concentration in CA was waist circumference (Table 2). In AA, BMI was the best surrogate for HOMA-IR. For fasting insulin concentration, percent body fat was the best marker in AA. None of the surrogate markers in AA had area under the ROC curve greater than 0.75.

DISCUSSION

The current study examined the appropriateness of using TG and TG/HDL-C as surrogates of insulin resistance in CA and AA. Our findings showed that even though more AA were insulin resistant, a significantly lower percentage of AA met the proposed cutoffs for high TG and TG/HDL-C. Furthermore, the predictability of insulin resistance when using TG and TG/HDL-C was poor in AA. The poor sensitivity noted in predicting insulin resistance in AA may reflect a non-relationship between TG and TG/HDL-C with HOMA-IR or fasting insulin concentrations, as also suggested by others (18). However, the correlations between TG and TG/HDL-C with HOMA-IR and fasting insulin concentrations were similar for both CA and AA (r for TG & HOMA-IR: CA = 0.30 & AA = 0.30; TG & Fasting Insulin: CA = 0.28 & AA = 0.27; TG/HDL-C & HOMA-IR: CA = 0.34 & AA = 0.33; and TG/HDL-C & Fasting Insulin: CA = 0.32 & AA = 0.29, and all associations, $p < .05$). Thus, the appropriateness of the cutoffs for TG and TG/HDL-C may be an issue, rather than the lack of correlation between these variables across ethnic groups.

Another commonly used surrogate for insulin resistance is abdominal obesity (6, 19, 20), In fact, the National Cholesterol Education program (NCEP) Adult Treatment Panel III (ATP-III) diagnostic criteria for metabolic syndrome uses waist circumference

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as a surrogate for insulin resistance. However, our study indicates while waist circumference was an excellent predictor of insulin resistance in CA, it is not as predictive of insulin resistance in AA. Rather, BMI for HOMA-IR and percent body fat for fasting insulin concentrations were the best anthropometric predictors in AA. Thus, neither the lipid criteria nor the waist circumference criteria appear adequate in predicting insulin resistance for AA men and women.

Defining insulin resistance is difficult because no clear guidelines or cutoffs for exist for either HOMA-IR or fasting insulin concentrations. The gold standard for diagnosing insulin resistance is the glucose clamp method, which is invasive and time consuming and not practical in a clinical setting. Thus the use of other related markers, such as TG or TG/HDL-C, has been encouraged. However, considering the poor predictive value of lipid markers and waist circumference in AA, other surrogates of insulin resistance such as HOMA-IR or fasting insulin concentration may be preferable in a clinical setting. The literature suggests that fasting insulin concentration is the best marker of insulin resistance, as determined by the clamp method (18, 21). Efforts should be undertaken to determine appropriate cutoffs for fasting insulin concentration and/or HOMA-IR as markers of insulin resistance so that they can be included as criteria for metabolic syndrome. This may help to identify AA with CVD predisposition and eliminate ethnic specific differences found in metabolic syndrome rates when using the current criteria.

The major limitation of this study was the relatively small sample size and the stringent inclusion and exclusion criteria. We included only healthy adults with BMI ≤ 38 kg/m2, thus generalizability may be only limited to relatively healthy normal weight to obese category I individuals. However, if the intent of these criteria/surrogates is early

detection, then our finding can be generalized to typical healthy population without any major illness. Another limitation of the study was our failure to use a glucose clamp, an insulin suppression test, or the frequently sampled intravenous glucose tolerance test. However, we used fasting insulin concentration and HOMA-IR to demonstrate the practical usage of insulin resistance in clinical settings. Fasting insulin and HOMA-IR are easy to use, take minimal time are not invasive, and show excellent predictability for insulin resistance as defined by the clamp method (18).

In summary, it is important to note that if TG and/or TG/HDL-C are to be used as surrogates for insulin resistance, they show moderate predictability in CA and poor predictability in AA. Our findings indicate that the relationship between lipids and insulin may differ by ethnicity; insulin resistance and/or metabolic syndrome will be under-diagnosed in seemingly healthy in AA if lipids parameters are used. Studies of CVD risk factors should be stratified by ethnicity to make accurate predictions and effective interventions.

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FIGURE LEGENDS

Figure 1. Receiver Operating Characteristic (ROC) Curves of Triglycerides (TG) and Triglycerides to HDL-C ratio (TG/HDL-C) Predicting Insulin Resistance by Ethnicity

Note: ROC curve of TG and TG/HDL for predicting HOMA-IR in CA (A) and in AA (B).

ROC curve of TG and TG/HDL for predicting fasting insulin concentrations in CA (C) and in AA (D).

TABLES

Table 1. Participant Characteristics by Ethnicity

|	Caucasians Mean (± SD) n = 50	African Americans Mean (± SD) n = 99
DEMOGRAPHICS		
Age (yrs) *	28.2 (5.5)	30.8 (8.2)
Gender (female/male)	24/26	54/45
Income		
< 25	7	26
25-50	17	42
50-80	12	20
>80K	8	7
Missing or Would not Say	6	5
Education		
HS	0	6
Some College	19	47
>BA/BS	25	42
Missing or Would not Say	6	5
ANTHROPOMETRICS		
Height (cm)	173.3 (10.4)	170.1 (10.2)
Weight (kg)	83.3 (19.4)	80.4 (16.8)
BMI (kg/m^2)	27.5 (5.2)	27.6 (4.5)
BMI Groups (NW/OW/OB)	18/15/17	31/34/34
Waist Circumference (cm)	88.1 (15.4)	87.7 (12.0)
Body Fat %	30.5 (9.6)	31.9 (8.2)
METABOLIC CHARACTERISTICS		
Fasting Glucose (mmol/L)	5.3 (.7)	5.1 (.7)
Fasting Insulin (µU/mL) *	10.2 (7.5)	12.4 (7.8)
HOMA-IR	2.4 (1.9)	2.9 (2.0)
Systolic BP (mm Hg)	123 (11.4)	124 (13.0)
Diastolic BP (mm Hg)	68 (8.6)	69 (9.1)
Total Cholesterol	155.1 (34.0)	155.8 (24.8)
Triglycerides (mg/dL) ***	105.4 (55.2)	68.2 (43.3)
HDL-C (mg/dL) *	42.5 (11.3)	46.9 (12.5)
LDL-C (mg/dL)	91.5 (30.9)	95.3 (23.0)
Triglycerides/HDL-C ***	2.8 (1.8)	1.8 (2.1)

Note: Ethnic differences significant at * $p < .05$; ** $p < .01$; *** $p < .001$

Table 2. Area Under Receiver Operating Characteristic Curves for Potential Markers of HOMA-IR and Fasting Insulin

Predicting	Variable	Caucasians		African Americans	
		Area Under ROC curve MEAN ± SE	95% Confidence Interval	Area Under ROC curve MEAN ± SE	95% Confidence Interval
HOMA-IR	Total Cholesterol	.626 ± .082	.466 - .785	.554 ± .059	.438 - .670
	TG	.763 ± .074[a]	.618 - .907	.625 ± .056[b]	.516 - .735
	HDL-C	.309 ± .076	.160 - .459	.379 ± .058	.266 - .492
	LDL-C	.576 ± .087	.404 - .747	.585 ± .058	.471 - .699
	TG/HDL-C Ratio	.772 ± .073[a]	.629 - .915	.639 ± .055[b]	.531 - .747
	BMI	.866 ± .053	.762 - .970	.696 ± .053	.592 - .801
	Waist	.923 ± .039	.847 - 1.00	.671 ± .058	.557 - .786
	Body Fat %	.744 ± .077	.592 - .896	.649 ± .059	.533 - .765
Fasting Insulin	Total Cholesterol	.660 ± .088	.488 - .832	.556 ± .064	.430 - .681
	TG	.770 ± .084[c]	.606 - .935	.633 ± .056[d]	.523 - .743
	HDL-C	.350 ± .084	.185 - .515	.371 ± .062	.248 - .493
	LDL-C	.590 ± .100	.395 - .786	.579 ± .055	.459 - .699
	TG/HDL-C Ratio	.765 ± .083[c]	.603 - .928	.651 ± .055[d]	.543 - .759
	BMI	.906 ± .052	.804 - 1.00	.712 ± .055	.605 - .819
	Waist	.910 ± .044	.823 - .996	.691 ± .057	.579 - .803
	Body Fat %	.840 ± .064	.714 - .967	.715 ± .058	.601 - .828

Note: [a] Corresponds to Figure 1A; [b] Figure B; [c] Figure C; and [d] Figure D

Figure 1.

C. CA

D. AA

1 - Specificity

19
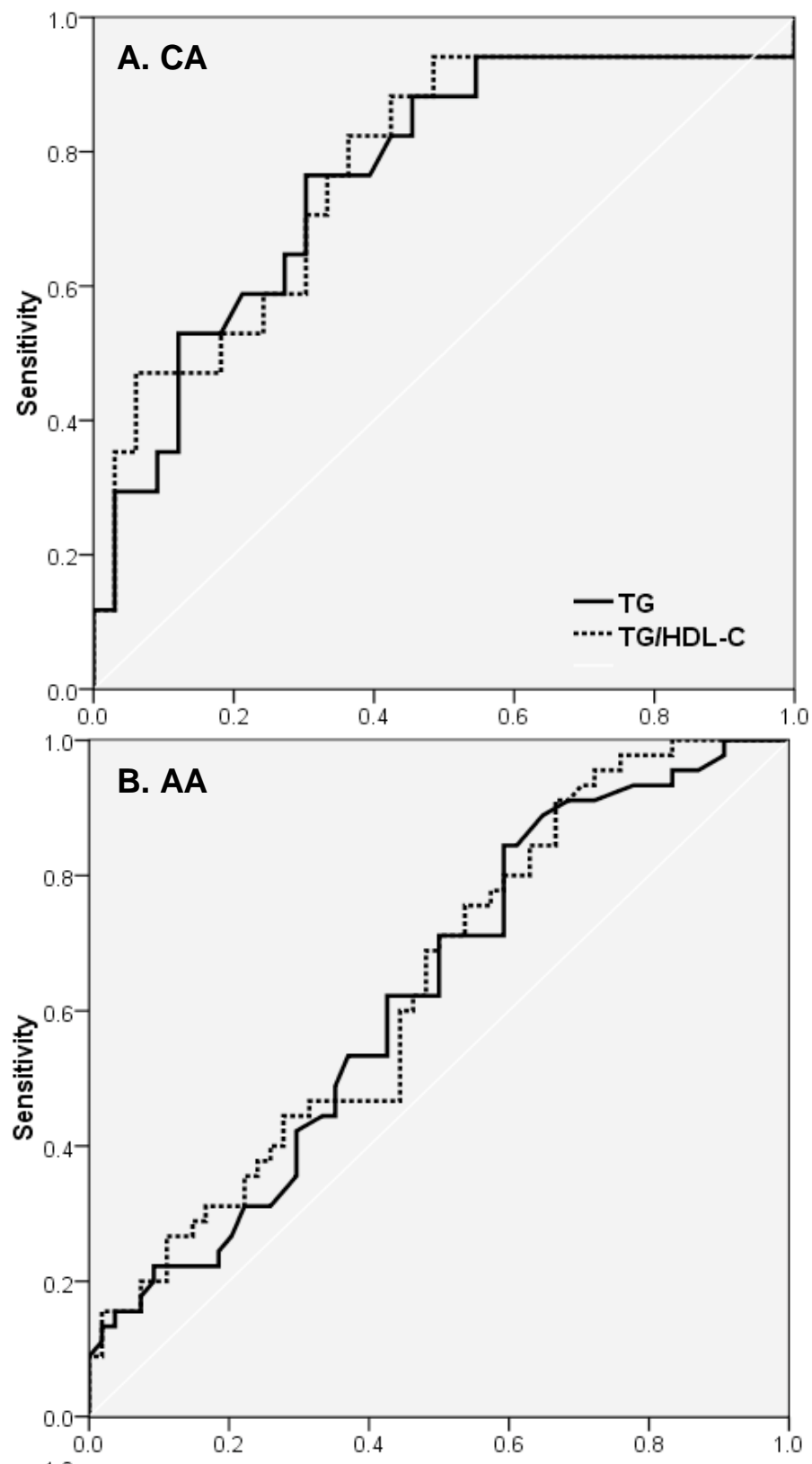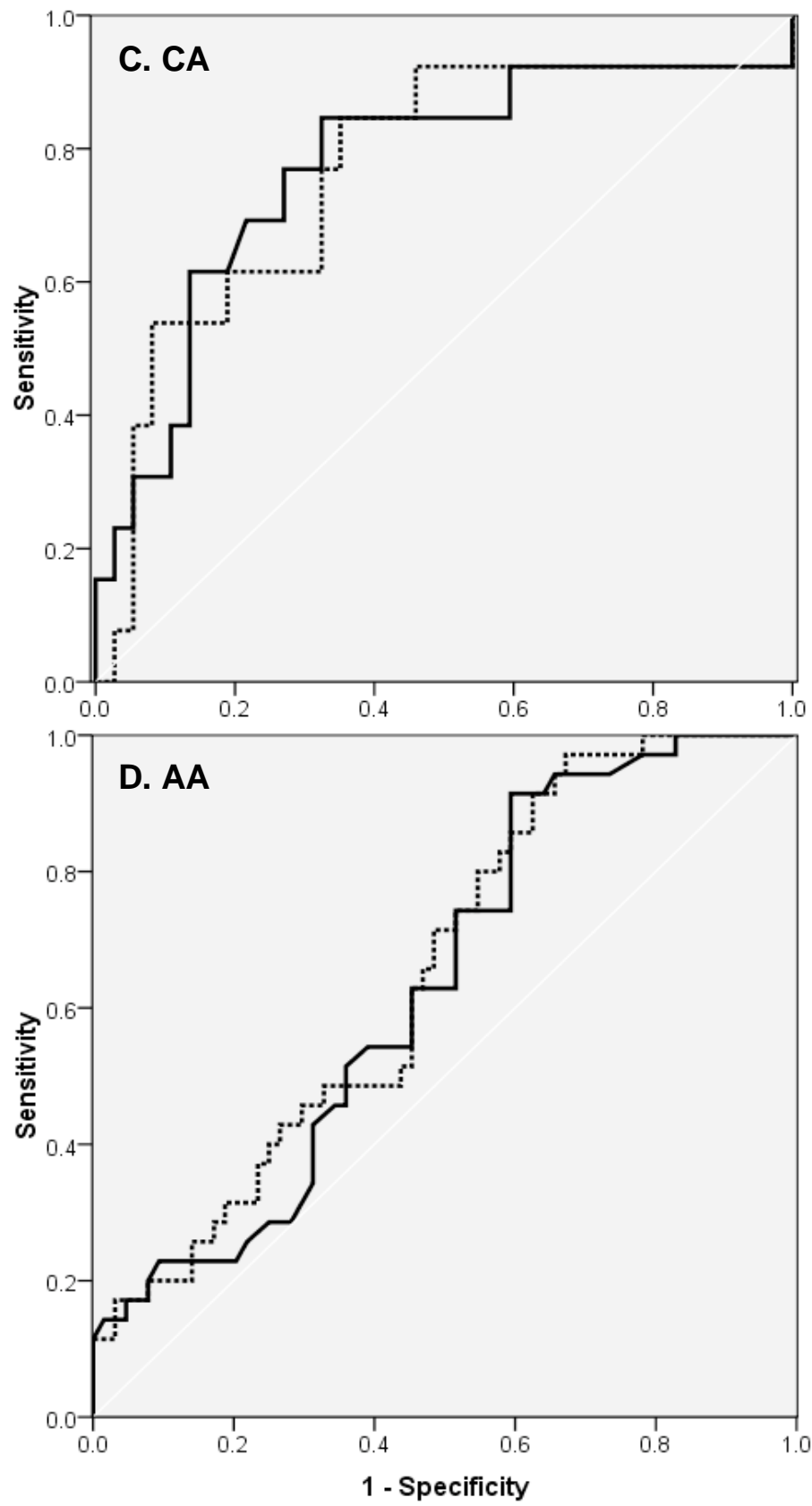
Diagnostic Criteria for Metabolic Syndrome: Caucasians versus African-Americans

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ABSTRACT

Background: Metabolic syndrome (MS) is a constellation of risk factors used by physicians to identify individuals at greatest risk for developing cardiovascular disease (CVD). An early diagnosis of CVD would benefit African-Americans (AA), who have a higher prevalence of and mortality rate from CVD compared to Caucasians (CA).

Purpose: We compared how two definitions for MS classified healthy CA and AA, and evaluated how including other CVD risk factors (C-Reactive Protein/CRP, percent body fat, fitness level, insulin resistance, and non-HDL cholesterol) changed the number of persons classified as MS.

Methods: Healthy AA (n=97) and CA (n=51) ranging from normal-weight to obese, 18 to 45 years, with neither hypertension nor diabetes, were evaluated for cardiorespiratory fitness, height, weight, percent body fat, hip and waist circumference, blood pressure (BP), and fasting blood glucose, insulin, triglycerides, HDL and non-HDL cholesterol, and CRP. Participants were classified as meeting the criteria for MS according to the National Cholesterol Education Program-Adult Treatment Panel III 2004 (ATP04) and the International Diabetes Federation (IDF) definitions.

Results: Significant ethnic differences ($p<0.01$) in classification were noted for both MS definitions (ATPO4: CA=16.7% vs. AA=5.7% and IDF: CA=23.5% vs. AA=8.2%). Ethnic differences were eliminated when either fitness level (ATP04: CA=27.1% vs. AA=19.3% and IDF: CA=29.4% vs. AA=28.6%) or percent body fat (ATPO4: CA=35.3% vs. AA=22.7% and IDF: CA=37.3% vs. AA=32.0%) was included as a criterion.

Conclusions: If diagnosis of MS is intended for early recognition of CVD risk and slowing CVD development, current definitions for MS will not capture apparently healthy AA. Either criterion suitable for AA need to be developed or health care providers need to consider assessing percent body fat and asking about participation in regular exercise. These two criterions would help identify AA at risk for CVD. More research is needed to identify risk factors specific to AA.

INTRODUCTION

Metabolic syndrome (MS), which affects nearly one-fourth of the US population (Ford *et al.* 2002), is a constellation of multiple risk factors used for early identification of individuals at risk for developing cardiovascular and/or coronary heart disease (CVD/CHD) (Grundy *et al.* 2004, Eckel *et al.* 2005, Grundy *et al.* 2005, Grundy *et al.* 2006, Assmann *et al.* 2007, Strazzullo *et al.* 2008). A diagnosis of MS permits early recognition of increased risk of CVD and allows health care providers to aggressively slow the development of CVD in African-Americans (AA) have a higher prevalence of insulin resistance, diabetes mellitus, hypertension, obesity and obesity-related conditions, and a higher rate of mortality from CVD than Caucasians (CA) (Williams *et al.* 2006, CDC 2007, Miller *et al.* 2008). Thus, early identification of MS in AA would be critical for slowing the development of CVD in this very high-risk population.

Currently, a variety of definitions for MS exist (Grundy *et al.* 2004, Eckel *et al.* 2005, Grundy *et al.* 2005, Grundy *et al.* 2006, Assmann *et al.* 2007, Strazzullo *et al.* 2008), but new research suggests that risk factors specific to a particular racial or ethnic population may be important. For example, dyslipidemia is included as a potential risk factor for all definitions of MS (Grundy *et al.* 2004, Eckel *et al.* 2005, Grundy *et al.* 2005, Grundy *et al.* 2006, Assmann *et al.* 2007, Strazzullo *et al.* 2008), yet recent studies indicate AA have more favorable lipid profiles than CA, despite higher rates of CVD (Kelley *et al.* 1999, Hall *et al.* 2003). In addition, Sumner et al. (Sumner and Cowie 2008) reported that insulin resistance in AA may require a different cut-off value for waist circumference (WC) than indicated by one MS definition (Okosun *et al.* 2000, Perry *et al.* 2008). Also most definitions of MS include waist circumference, but distinct cut-offs have been suggested for different ethnic groups. In contrast, C-reactive protein (CRP) is not included in any of the current definitions for MS (Grundy *et al.*

2004, Eckel *et al.* 2005, Grundy *et al.* 2005, Grundy *et al.* 2006, Assmann *et al.* 2007, Strazzullo *et al.* 2008), even though a proinflammatory state is considered a component of MS and an elevated CRP is associated with increased risk of CHD (LaMonte *et al.* 2002, Aronson *et al.* 2004a, Kelley-Hedgepeth *et al.* 2008). Ethnic differences in CRP have been reported, but no ethnic-specific cut-offs have been identified. Regardless of ethnicity, it has been suggested that CRP should be a criterion for MS due to its predictive value for CHD and new onset diabetes (Sattar *et al.* 2003).

Based on a non-diabetic study population, we chose two guidelines for MS: The National Cholesterol Education Program, Adult Therapy Panel III, 2004 version (ATP04), and the International Diabetes Federation (IDF) Epidemiology Task Force Consensus Group, and examined the proportion of CA and AA meeting these two definitions for MS. Our objectives were to 1) determine whether the current criteria for MS are appropriate for early identification of CHD or diabetes when applied to a seemingly healthy sample of AA between 18 and 45 years of age; 2) evaluate how risk assignment using these criteria in AA compared to its use in a sample of age-, weight-, and health- matched CA; and 3) determine how the percentage of persons assigned as high risk with MS changed when other known risk factors for CHD were included in as a criterion measure for MS. The additional risk factors included CRP, aerobic fitness level, percent body fat, surrogates for insulin resistance, and non-HDL cholesterol.

MATERIALS AND METHODS

Subject Population

All participants were informed of the purposes and procedures of the study and provided written consent prior to participation. This study was approved and monitored by the Uniformed Services University of the Health Sciences Institutional Review Board, and was part of a larger

study. Of the 160 volunteers, data for 97 AA participants (44 males; 53 females) and 51 CA

particpants (27 males; 24 females) were available for the analyses. Participants met the following

inclusionary criteria to particpate: 1) 18-45 years of age; 2) body mass index (BMI) between 18-

38 kg/m^2; 3) blood pressure ≤139 and ≤89 mm Hg; 4) not using blood pressure regulators,

glucose lowering agents, antidepressant/psychotropic drugs or glucocorticoids; 5) fasting blood

glucose < 5.6 mmol/L; and, 6) had to self report as either a CA or AA. Participants were also free

of other known major diseases, such as heart disease, diabetes mellitus, peripheral vascular

disease, liver disease, thyroid and other endocrine diseases. Each volunteer underwent a

thorough telephone health screening and an on-site medical examination to ensure that the

inclusion/exclusion criteria were met. Participants were recruited by body mass index (BMI) so

we would have a comparable distribution among normal weight, overweight and obese

participants. Among all participants, 18 AA (19.8%) and 12 CA (23.5%) were either current

smokers or had smoked in the past.

Procedures/Measurements

Participant assessments included anthropometric measures (weight, height, waist

circumference, and percent body fat) and resting blood pressure. Blood measures include:

glucose, insulin, lipids (cholesterol, tryglycerides, HDL, calculated LDL and non-HDL

cholesterol) and high sensitivity C-reactive protein (CRP) measures after an 8-hour fast. Fasting

blood glucose and insulin were used to estimate insulin sensitivity by the Homeostasis Model

Assessment (HOMA) (Matthews *et al.* 1985). Body weight was measured with a calibrated

balance beam metric scale to the nearest 0.1kg, and height was measured to the nearest 0.1cm

while the participant was wearing light clothing and no shoes. BMI was calculated from weight

and height (weight in kg divided by height in meters squared), and percent body fat was

calculated from bioelectric impedance (BIA) measures using the NHANES formula (Chumlea *et al.* 2002). Waist circumference was measured with an inelastic tape around the waist by standard techniques. After a one-hour rest, blood pressure was taken in the supine position with the Criticare Systems automatic blood pressure machine (Model 506N3; Waukesha, WI).

Blood was collected in fasting state by standardized venipuncture techniques between 0700 and 0900 h. Samples were collected with anticoagulant for insulin, lipid profiles, and CRP, and in sodium flouride tubes for glucose. Plasma was extracted and stored in a -80°C freezer. Blood glucose concentration was assessed with the YSI Biochemistry Analyzer Model 2700/115V (Yellow Springs Instrument Co., Inc., Yellow Springs, OH). Plasma insulin was measured by standard radioimmunoassay (Diagnostic Systems Laboratory-1600; Webster, TX). Insulin samples were assayed in duplicate and samples with an insulin concentration greater than 22-25 µIU/mL were diluted and re-tested. Intra- and inter-assay coefficients of variation were <10 %. All samples were within 0.2 µIU/mL apart or a third sample was measured; the closest two measurements were used. Upon study completion, all samples were taken to the National Institutes of Health Department of Laboratory Medicine for lipid profile testing (cholesterol, triglycerides, HDL, LDL) and high sensitivity CRP analyses with the Immulite 2500 Analyzer (Siemens Medical Solutions Diagnostics, Erlangen, Germany). Low density lipoprotein-cholestreol (LDL-C) was calculated by the Friedewald equasion and non-HDL cholesterol was the total cholesterol minus HDL-C.

Cardiovascular Fitness Test

Each participant underwent a maximal aerobic graded exercise test ($VO_{2\ max}$ test) on a treadmill (Philips StressVue Exercise Stress Testing System with Trackmaster Full Vision Inc. Treadmill; Waltham, MA) to assess cardiorespiratory fitness. The $VO_{2\ max}$ test was supervised by

an exercise specialist and followed standarized testing procedures as outlined by the American College of Sports Medicine and other experienced investigators (McKay and Banister 1976, Buchfuhrer *et al.* 1983). The test used in this investigation was a modification of a protocol previously described by Kyle et al. (Kyle *et al.* 1989) from our laboratory. In brief, the $VO_{2\,max}$ test began with a 5 min. warm-up at a speed of 4.3 kph and a 2% grade. After the warm-up phase, participants walked/ran at a constant speed of 4.3 to 11.3 kph, depending on the heart rate achieved during warm-up; the incline started at 0% and was increased 2.5% every two minutes until the participant reached volitional fatigue or exhibited a plateau in VO_2 with an increase in workload. Participants were categorized into one of five fitness groups as noted by the American College of Sports Medicine - low, fair, average, good, and high - based on their gender, age, and relative VO_{2max} value (2006).

Metabolic Syndrome Classification Strategies

Participants were classified as having MS by two separate definitions: The National Cholesterol Education Program-Adult Treatment Panel III 2004 version (ATP04) and the International Diabetes Federation (IDF) (Table 1). Because we had recruited equal number of participants in each BMI category, we defined obesity based on percent body fat (De Lorenzo *et al.* 2003). Men with percent body fat of $\geq 25\%$ and women with $\geq 35\%$ were defined as obese (De Lorenzo *et al.* 2003). Other criteria included CRP levels ≥ 9.52 mmol/L (Ridker 2003), non-HDL cholesterol (≥ 4.1 mmol/L), fitness in the low to fair category, and HOMA IR ≥ 2.3 for women and ≥ 2.7 for men. When percent body fat was used for identifying high risk, it was used without WC so that obesity was not given double weight for importance.

Statistical Analyses

Standard descriptive statistics were used to compare baseline characteristics using mean and SD. *Chi*-squared analyses and 2 (ethnicity) x 2 (gender) multivariate analysis of variance (MANOVA) techniques were used to analyze demographic variables and CHD risk factors. Data were natural log transformed to normalize, and analyses were performed on the transformed data, although untransformed data are presented in the tables. The statistical significance level was set at $< .05$, and all data analyses were conducted with SPSS 15.0 (SPSS, version 16.0.1; SPSS, Inc., Chicago, IL).

RESULTS

Participants Characteristics

Table 2 summarizes the characteristics of the participants by ethnicity and gender. Participants were comparable in age and female to male ratio (AA=97; CA=51). There were no ethnicity and gender interactions and no ethnicity difference for anthropometric measurements. In contrast, gender differences were noted, as expected: women had lower body weight, waist circumferences and VO_{2max} (fitness), and higher percent body fat, s compared to men. The majority of the AA population had suboptimal cardiorespiratory fitness: VO_{2max}, was significantly lower in both AA men and women relative to CA men and women. Additionally, AA had higher fasting insulin concentrations than CA, despite comparable fasting glucose and HOMA values. Ethnicity and gender interactions were noted for total cholesterol and triglycerides (TG): total cholesterol was lowest in CA men and highest in CA women. Triglycerides were lowest among AA women followed by AA men, and significantly higher in

CA men and women. HDL was significantly higher in AA than CA and higher in women in general: AA women had the highest HDL concentrations.

Metabolic Syndrome

Figure 1 presents the percentage of CA and AA who met the criteria for MS based on the ATP04 and IDF definitions and how the definition of risk changed when other criteria were included. Only 5.7% of AA as compared to 16.7% of CA were categorized as having MS by the ATP04 criteria. This increased to 8.2% for AA and 23.5% for CA when the IDF criteria were used: significantly fewer AA meet the criteria than CA for both definitions ($p < 0.01$). When fitness, CRP, percent body fat and/or HOMA were included in the list as possible high risk criterion, the percentage meeting the definition increased in both AA and CA, and ethnic differences were eliminated. In contrast, significant ethnic differences remained when non-HDL cholesterol was included as a criterion in either definition. According to ATP04 criterion for waist circumference (WC ≥102 or ≥88 cm), 31% of AA and 29.2% of CA exceeded the cut-off; this distribution increased to 51.7% of AA and 50.0% of CA when the IDF criterion was used (WC ≥ 94 or 80 cm for men and women, respectively). Importantly, no AA or CA meeting the ATP04 or IDF criteria for MS were in the good to high fitness categories.

Figure 2 presents the percent of those meeting the respective individuals at risk for MS criteria and CVD risk factors by ethnicity. Ethnic-specific differences were observed for triglycerides, HDL, non-HDL, and fitness. As indicated in Figure 2, 3.1% and 48.5% of AA met the criteria for high triglycerides and low HDL, respectively, as compared to 25.5% and 60.8% of CA. Likewise, 3.1% and 57.1% of AA met the criteria for non-HDL and fitness as compared to 12.0% and 31.4% of CA. Thus, non-HDL and triglycerides are not indicative of MS in AA.

DISCUSSION

Our study and the current literature (Ford *et al.* 2002, Hall *et al.* 2003) support the finding: AA appear healthier than CA when MS criteria are used to qualify health. However, when selected criteria were added to those in the current definitions (ATP04 and IDF), the number of AA at-risk increased significantly, such that ethnic differences were eliminated. The critical criterion for removing ethnic differences included fitness and HOMA. Given that AA have the highest rate of mortality from CVD and CHD, the definitions for risk, according to current MS criteria, may not be suitable for apparently healthy AA between 18 and 45 years of age. Early recognition of increased risk of CVD and the opportunity to aggressively slow the development of CVD would be overlooked with the current definitions.

The Adult Treatment Panel III and the International Diabetes Federation criteria for metabolic syndrome are not vastly different from each other. Unlike several other definitions, these two particular classifications focus on diagnosing those with multiple risk factors for CVD, rather than relying solely on insulin resistance. The ATP04 gives equal weight to each of the criterion whereas the IDF requires one essential criterion, waist circumference, to be met. Thus, the IDF definition places the highest priority on abdominal obesity as a surrogate for insulin resistance, and assigns the other criterion a lower priority (Grundy *et al.* 2005). In contrast, the ATP04 definition weighs each criteria equally (Reaven 2006).

We included percent body fat as one of the high-risk criterion because excess fat is associated with increased morbidity and mortality (Carroll *et al.* 2008, Perry *et al.* 2008). Although waist circumference is a useful measure of abdominal obesity and BMI is a reasonable surrogate of obesity, both measures have limitations. Waist circumference has been shown to differ significantly as a function of the four commonly used anatomic sites (Wang *et al.* 2003),

and many men and women who are obese according to percent body fat, are not be classified as obese based on BMI (De Lorenzo *et al.* 2003). Percent body fat may be a better measure of obesity, and is highly correlated with both waist circumference and BMI (Carroll *et al.* 2008, Heinrich *et al.* 2008). In the present study, 50% of CA and 71% of AA classified as overweight by BMI were obese by percent body fat. In addition, 30.3% of CA and 51.7% of AA with waist circumferences below the ATP04 cut-off and 8.7% of CA and 31.0% of AA with waist circumferences below the IDF cut-off were classified as obese when percent fat was used. Importantly, including percent body fat significantly increased the number of AA and CA recognized as at risk and eliminated the ethnic differences in risk assignment..

We considered several other criterions currently not included as part of the MS definition - fitness, CRP, and HOMA; and including any of these eliminated the ethnic difference in risk classification. It is recognized that cardiorespiratory fitness is neither easy nor simple to quantify, but simply asking about exercise and/or physical activity habits may be adequate. Such information would be important, because physical activity and regular exercise have independent actions with regard to reducing the risk of CHD (Bauman and Owen 1991, LaMonte *et al.* 2002, Simmons 2008). Physical activity is a frontline approach for treating CHD and other chronic diseases. In cross sectional studies on adolescents, low cardiovascular fitness ($VO_{2\ max}$), low physical activity, and a sedentary lifestyle are associated with MS (Torok *et al.* 2001, Ventura *et al.* 2006, Kelishadi *et al.* 2007, Rizzo *et al.* 2007). In addition, physical inactivity or a sedentary lifestyle and poor cardiorespiratory fitness are associated with an increase in other chronic diseases, including type 2 diabetes mellitus (Helmrich *et al.* 1991, Manson *et al.* 1991, Lynch *et al.* 1996, Orakzai *et al.* 2006) and CHD (Lakka *et al.* 1994, Laukkanen *et al.* 2001, Orakzai *et al.* 2006). Importantly, Laaksonen (Laaksonen *et al.* 2002) concluded that moderate and vigorous

physical activity decreased the risk of MS by nearly two thirds in a population of middle-aged men. The current non-medical treatment of MS is lifestyle change through physical activity (Orakzai *et al.* 2006), but the guidelines for changing from high risk status should be given as a 'prescription' to patients.

With regard to CRP and HOMA, both have promise, but will require more research. CRP has been associated with obesity, CVD, insulin resistance, and physical fitness (Aronson *et al.* 2004b, LaMonte *et al.* 2005, Forouhi and Sattar 2006, de Ferranti and Rifai 2007, Hyatt *et al.* 2008, Kelley-Hedgepeth *et al.* 2008, Hamer and Steptoe 2009). However, day-to-day variability in CRP and levels that reflect CVD need to be established before including it as a valid criterion. Additionally, several reports suggest ethnic differences in CRP, which may limit its usefulness (LaMonte *et al.* 2005, Meng *et al.* 2007, Kelley-Hedgepeth *et al.* 2008, Leung *et al.* 2008, Miller *et al.* 2008). As for HOMA, no established cut-off values are available, except those proposed by Oterdoom et al. (Oterdoom *et al.* 2008). Their cut-offs were used in the present study and this measure identified significantly more CA and AA than the ATP04 and IDF criteria alone. At present HOMA is neither difficult nor time-consuming to calculate, and could become a criterion measure for high-risk status. Clearly more research will be needed.

It is acknowledged that our study has several limitations. First, the subjects in this study do not truly represent the overweight and obese AA population because of our restrictive inclusion/exclusion criteria. However, if the goal of using diagnostic criteria of MS is early detection and aggressive intervention to prevent disease, these data have profound implications as the current definitions may not accurately reflect risk for AA. Secondly, although our percent body fat values may overestimate actual body fat in AA, we used the NHANES equation to

avoid any potential ethnic bias. Finally, our definition of obesity (>25% for men and > 35% for women) seems very liberal, which means that those identified as obese, should be obese.

Overall, fitness, percent body fat, CRP, and HOMA identified significantly more potentially at risk persons than the current ATP04 and IDF definitions. They also eliminated the ethnic differences in classification. These data provide strong evidence that either ethnic-specific criteria should be developed, or that the current criteria are not appropriate for certain populations. Importantly, with respect to fitness, CVD risk, and MS, the common theme is excess body fat; the importance of other variables depends on ethnicity and perhaps lifestyle behaviors.

In summary, our data demonstrate and confirm that the use of current criteria for MS is biased against AA, such that early identification of risk may not be achieved. If the intention of diagnosing MS is early recognition of increased CVD risk so aggressive measures can be targeted to slow progression of CVD, then other approaches for identifying those at risk should be considered. In particular, percent body fat and fitness are potential high-risk measures. Health care providers can ask about participation in regular physical exercise and estimate percent body fat without difficulty. If percent body fat is > 35% for women and > 25% for men, and no regular physical activity is reported, then risk for CVD should be assumed for AA. Early diagnosis can and should be used to promote lifestyle changes in physical activity and reducing body fat. Lastly, more research is needed to identify other specific various factors that determine risk of CVD and diabetes in AA.

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FIGURE LEGENDS

Figure 1.   Percent of CA and AA meeting ATP04 and IDF criteria for Metabolic Syndrome and the increase in prevalence when high risk criteria included CRP ($\geq$ 9.52 mmol/L), body fat ($\geq$ 25% for men and 35% for women), low to fair fitness, HOMA > 2.3 for women/2.7 for men, or non-HDL > 4.1 mmol/L, as one of the 3 or 2 criteria for the ATP04 and IDF, respectively. Significant Ethnic Differences: *p < .05; ** p < .01

Figure 2.   Percent of CA and AA meeting the respective individual MS and other high risk criterion for Metabolic Syndrome by ethnicity. Significant Ethnic Differences: *p < .05; ** p < .01

Table 1. Two Definitions of Metabolic Syndrome

Criteria	ATP III (2004)	IDF (2005)
Special Instructions	Any 3 of the following 5 features:	Meet Waist Circumference criteria + any two of the criteria below WC.
Waist Circumference	Male WC ≥ 102 cm Female WC ≥ 88 cm	*Male WC ≥ 94 cm Female WC ≥ 80 cm
Blood Pressure	≥130 and/or ≥85 mm Hg or on hypertension medications	≥130 and/or ≥85 mm Hg or on hypertension medications
Glucose	>5.6 mmol/L (includes diabetes)	>5.6 mmol/L (includes diabetes)
Lipids	TG >1.7 mmol/L	TG ≥1.7 mmol/L or on TG Rx
	HDL-C <1.036 mmol/L for men or <1.295 mmol/L for women	HDL-C <1.036 mmol/L for men or <1.295 mmol/L for women, or on HDL-C Rx

*WC based on European (Caucasian) measurements

Table 2. Participant Characteristics by Ethnicity and Gender

	African-Americans n = 97		Caucasians n=51	
	Male Mean ± SD	**Female** Mean ± SD	**Male** Mean ± SD	**Female** Mean ± SD
Demographics				
Age (yrs)	30.7 ± 8.5	30.9 ± 8.0	27.9 ± 5.3	28.9 ± 5.8
Gender (female/male)	44	53	27	24
Anthropometric Measures				
Weight §§§	87.9 ± 15.3	73.9 ± 15.6	90.6 ± 17.1	75.7 ± 18.9
Body Fat% §§§	26.1 ± 5.0	30.4 ± 9.5	24.5 ± 7.4	35.9 ± 8.6
Body Mass Index	27.7 ± 4.0	27.4 ± 4.9	27.5 ± 4.7	27.6 ± 5.8
Waist Circumference (cm) §§	90.5 ± 11.7	85.1 ± 11.8	91.6 ± 12.8	84.2 ± 17.1
Hip Circumference (cm)	106.4 ± 10.1	107.5 ± 10.7	106.5 ± 10.0	108.3 ± 14.6
VO2max (ml/kg/min) ** §§§	42.0 ± 9.4	32.3 ± 9.0	46.5 ± 8.7	38.0 ± 9.8
Blood Pressure				
Systolic (mm Hg) §§§	128 ± 12.3	122 ± 13.1	127 ± 9.8	119 ± 11.6
Diastolic (mm Hg)	69 ± 7.5	68 ± 10.5	68 ± 8.9	67 ± 8.3
Glucose & Insulin Measures				
Fasting Glucose (mM)	5.2 ± 0.6	5.1 ± 1.0	5.5 ± 0.7	5.1 ± 0.6
Fasting Insulin (µU/mL) *	12.1 ± 8.7	12.7 ± 6.4	9.5 ± 5.3	11.3 ± 9.3
HOMA IR	2.8 ± 2.0	3.0 ± 1.8	2.3 ± 1.2	3.0 ± 3.1
Lipids				
Total Cholesterol (mmol/L)	4.1 ± 0.6	4.0 ± 0.6	3.8 ± 0.7	4.2 ± 1.1
Triglycerides (mmol/L) *** §	0.9 ± 0.5	0.6 ± 0.4	1.2 ± 0.7	1.2 ± 0.7
HDL (mmol/L) * §§§	1.1 ± 0.3	1.3 ± 0.3	0.9 ± 0.2	1.3 ± 0.3
LDL (mmol/L)	2.6 ± 0.6	2.3 ± 0.6	2.3 ± 0.7	2.4 ± 0.9
Non-HDL (mmol/L)	3.0 ± 0.6	2.6 ± 0.6	2.9 ± 0.7	2.9 ± 1.0
CRP (mmol/L**)**	15.24 ± 21.0	20.0 ± 27.6	14.3 ± 15.2	43.8 ± 43.8

Note: * Ethnic Differences Significant at $p < .05$; ** $p < .01$; *** $p < .001$

§ Gender Differences Significant at $p < .05$; §§ $p < .01$; §§§ $p < .001$

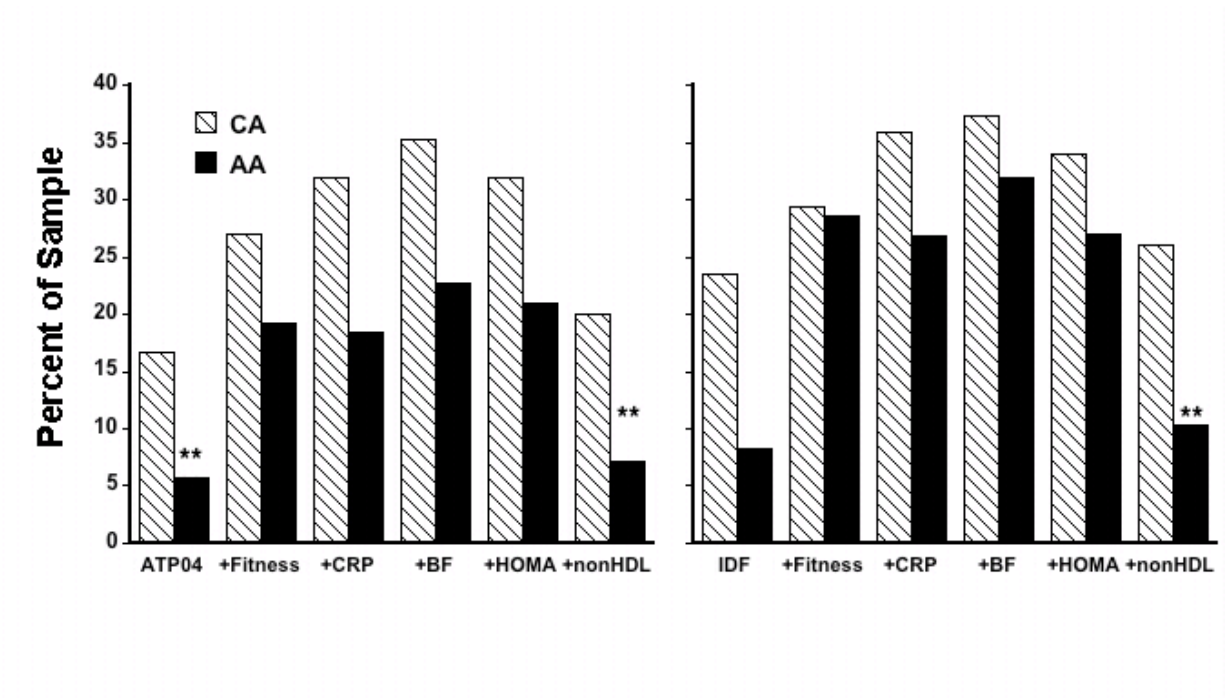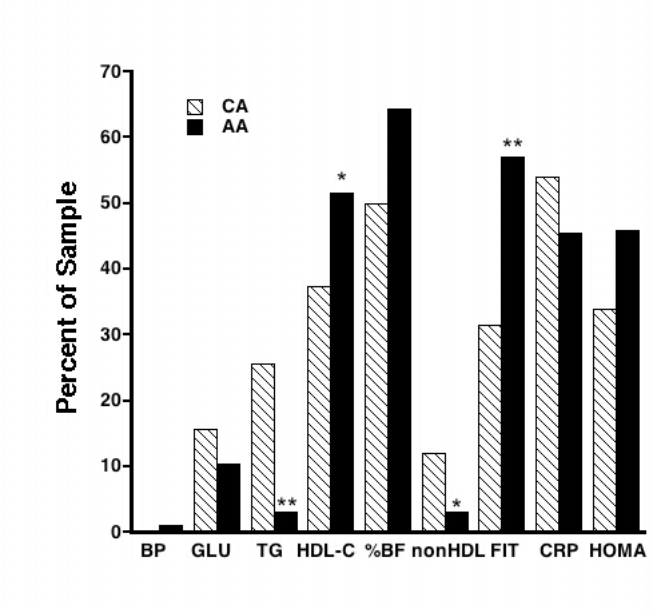Interaction Significant at $p < .05$

Figure 1.

Figure 2.

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Cardiovascular Fitness and Risk Factors

of Healthy African-Americans and Caucasians

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ABSTRACT

Purpose: African-Americans (AA) have a higher prevalence and rate of mortality from cardiovascular disease (CVD) than Caucasians (CA); one important risk factor for CVD is poor cardiovascular fitness. We quantified fitness and related primary risk factors for CVD as a function of fitness in healthy AA and CA.

Methods: Participants included healthy AA (n=91) and CA (n = 51) men and women with body-mass-index (BMI) <38 kg/m^2, 18~45 years of age, fasting blood glucose < 126 mg/dL and blood pressure measures < 140 and 90 mm Hg. Maximal aerobic power, fasting blood glucose, insulin, lipid profiles, C-Reactive Protein (CRP), waist and hip circumference, and percent body fat were measured.

Results: The majority of AA (57.1%) were categorized as low to fair fitness (Caucasian: 31.4%) and only 20.8% were of good to high fitness (Caucasian: 39.2%). Over 50% of subjects in the low-fair fitness category were at risk for CVD based on HDL-C, pre-hypertension, CRP, percent body fat, and BMI. Risk factors for CVD increased with decreasing fitness in both ethnic groups. Although CRP was lower in AA (1.8±0.3 mg/L) than CA (2.3±0.5 mg/L), it was negatively associated with fitness and positively associated with body fat for both groups. Regression analysis revealed that percent body fat and CRP were associated with low fitness in AA, and percent body fat, fasting glucose and diastolic pressure in CA.

Conclusions: Low fitness may characterize apparently "healthy" AA as at-risk for CVD. Including fitness as a risk factor for CVD would improve early identification of at-risk AA. Importantly, prescribing exercise as medicine and promoting regular physical activity to improve fitness is essential among AA, particularly AA women.

INTRODUCTION

African-Americans (AA) have a higher prevalence and rate of mortality from cardiovascular disease (CVD) than Caucasians (CA) (12, 24, 28), the highest age-adjusted prevalence of coronary heart disease (CHD), and higher death rates from stroke than any ethnic group in the United States (24). Hozawa et al. (15) suggested the higher incidence rate of CVD in AA may be largely attributable to a higher prevalence of risk factors and postulated that awareness of these risk factors might help eliminate the health disparity in CVD incidence.

Mosca et al. (30) showed that awareness of CVD as the leading cause of death was independently correlated with increased physical activity and weight loss in the previous year among women, and suggested that awareness of CVD may be important for primary prevention. Interestingly, Christian et al. (8) reported that awareness of CVD risk factors was significantly lower for AA and Hispanic women than CA women. Together these data suggest that awareness of elevated CVD risk factors in AA might lead to effective primary prevention and thus greatly reduce CVD occurrence, as it has in CA (30).

One strong predictor of all-cause and CVD mortality is cardiovascular fitness (4, 13, 17, 34, 37, 38). The strong inverse relationship between CVD death and cardiovascular fitness categories recently prompted Steven Blair (4) to suggest that physical inactivity may be one of the most important public health problems of the 21st century. Improvements in fitness correspond to reductions in blood pressure (34, 37), improvements in insulin sensitivity (13), and lower levels of C-reactive protein (CRP) (21, 22), and regular physical activity and exercise have independent actions for reducing the risk of CVD (22, 37). Even a modest increase in aerobic fitness level has been shown to have a significant impact on insulin sensitivity, lipoprotein

parameters and overall risks for CVD in sedentary overweight or obese African-American women (13).

Because of the important relation between fitness and CVD, we quantified maximal aerobic power, the primary index of cardiovascular fitness, and other CVD risk factors in a sample of seemingly healthy AA and CA. Specifically, we investigated fitness levels, the association between fitness and primary CVD risk factors, and determined the proportion of subjects meeting various standard criteria for CVD risk by fitness category.

METHODS

Subject Population

All participants were informed of the purposes and procedures and provided written consent prior to participation. This study was approved and monitored by the Uniformed Services University of the Health Sciences Institutional Review Board. Of the 160 volunteers, complete data for 91 AA participants (41 males; 50 females) and 51 CA particpants (27 males; 24 females) were available for analysis. Participants met the following inclusion criteria: 1) 18-45 years of age; 2) body mass index (BMI) between 18-38 kg/m^2; 3) blood pressure ≤139/≤89 mm Hg; 4) not using medications for hypertension or high glucose, antidepressant/psychotropic drugs or glucocorticoids; 5) fasting blood glucose < 126 mg/dL; and 6) self-reported as CA or AA. Participants were also free of other known major diseases, (CVD, diabetes, peripheral vascular, liver, and endocrine diseases). Each volunteer underwent a telephone health screening and on-site medical examination to ensure inclusion/exclusion criteria were met. Participants were recruited by BMI to achieve a comparable distribution between CA and AA of normal weight, overweight, and obese.

Procedures/Measurements

Participant assessments consisted of anthropometric measures (weight, height, waist and hip circumferences, and percent body fat), blood pressure, and blood draws for fasting blood glucose, insulin, lipid profiles (total cholesterol, tryglycerides, HDL-Cholesterol (HDL), calculated LDL-Cholesterol (LDL) and non-HDL-Cholesterol (non-HDL)) and high sensitivity C-Reactive Protein (CRP). BMI was calculated from the anthropometric measures as weight in kg divided by height^2 in meters, and percent body fat was calculated from bioelectric impedance by using the NHANES formula (9). After a one hour rest blood pressure was taken in the supine position with Criticare Systems automatic blood pressure machine (Model 506N3; Waukesha, WI).

Fasting blood was collected between 0700 and 0900 h. Samples were collected with anticoagulant for insulin, lipid profiles, and CRP, and in sodium flouride tubes for glucose. Plasma was extracted and stored in a -80˚C freezer. Blood glucose concentration was measured with the YSI Biochemistry Analyzer Model 2700/115V (Yellow Springs Instrument Co., Inc., Yellow Springs, OH). Serum insulin was measured by standard radioimmunoassay (Diagnostic Systems Laboratory-1600; Webster, TX). Fasting blood glucose and insulin were used to estimate insulin sensitivity by the Homeostasis Model Assessment (HOMA) [(glucose (mmol/L) × insulin (μU/mL))/22.5] (25).

Lipid profiles were determined at the National Institutes of Health Department of Laboratory Medicine using a LX-20 analyzer (Beckman, San Diego, CA) and CRP analyses with the Immulite 2500 Analyzer (Siemens Medical Solutions Diagnostics, Erlangen, Germany). LDL was calculated by the Friedewald equasion and non-HDL was calcualted as total cholesterol-HDL.

Maximal Aerobic Power Exercise Test (VO$_{2max}$ Test)

Each participant underwent a maximal aerobic power exercise test (VO$_{2\ max}$ test) on a treadmill (Philips StressVue Exercise Stress System, Trackmaster Full Vision Inc. Treadmill; Waltham, MA) to assess cardiovascular fitness. The VO$_{2\ max}$ test was supervised by an exercise specialist and followed standarized procedures as outlined by the American College of Sports Medicine (26). The test was a modification of a protocol previously described by Kyle et al. (19) from our laboratory. In brief, the VO$_{2\ max}$ test began with a 5 min warm-up at 3.0 mph and a 2% grade. After a warm-up, participants walked/ran at a constant speed of 3 to 7 mph, depending on the heart rate achieved during warm-up; the incline started at 0% and was increased 2.5% every two minutes until the participant reached volitional fatigue or exhibited a plateau in VO$_2$ with an increase in workload. Attainment of VO2max was determined by selected criteria: achieving a plateau or demonstrating a < 2.1 ml•kg^{-1}•min^{-1} increase with 2.5% grade or meeting three of the following four criteria: blood lactate ≥ 8 mmol/L, a respiratory exchange ratio ≥ 1.10, an increase in heart rate to 90% of age predicted maximal heart rate, and/or a rating of perceived exertion ≥ 17.

Classification Strategies

Based on relative VO$_{2max}$ value, gender, and age, subjects were categorized into one of three fitness groups as noted by the American College of Sports Medicine (1): low to fair (well below to below average), average, and good to high (above to well above average). They were also categorized as "at risk" or "not risk" for CVD based on criteria defined by various organizations and guidelines (3, 14). Specifically, risk factors included smoking status, lipoprotein profiles (total cholesterol > 200 mg/dL; triglycerides > 150 mg/dL; LDL cholesterol ≥ 130 mg/dL; HDL cholesterol <40 mg/dL for men or <50 mg/dL for women; non-HDL cholesterol ≥ 160 mg/dL),

anthropometric criteria (BMI > 30; waist circumference ≥ 94 cm for men and ≥ 88 cm for women; and percent body fat ≥ 25% and ≥ 35% for males and females, respectively) (11), CRP levels (> 1.0 mg/L) (10), pre-hypertension (≥ 120/80 and ≤ 139/89 mm Hg), and glucose (>100 mg/dL). We also classified subjects as obese or not obese based on percent fat (11). In this study, 33 of 88 subjects were obese by body fat measures, but not by BMI. Finally, HOMA values > 2.3 for women and >2.7 for men were considered a CVD risk factor based on the quartiles proposed by Oterdoom et al. (32). Each person was assigned a 1 (Yes) or 0 (No), based on meeting or not meeting the criteria and a total CVD risk score was calculated by summing all criteria. Percent body fat was used in the total score as the measure of obesity.

Statistical Analyses

Chi-squared analyses, multivariate analysis of variance (MANOVA), and ANOVA techniques were used to analyze demographic variables and CVD risk factors as a function of ethnicity and fitness category. Following MANOVA/ANOVA, *a priori* one-way ANOVAs were performed separately for CA and AA as a function of fitness category to address the differences on CVD variables based on fitness level for CA and AA. A hierarchical linear regression was performed to examine the primary variables contributing to cardiovascular fitness.

Data were normalized (CRP, insulin, total cholesterol, and triglyceride), and analyses were performed on transformed data, although untransformed data are presented. The statistical significance level was set at < 0.05, and data are presented as mean ± SEM. Data were analyzed using SPSS statistical package (SPSS, version 16.0.1; SPSS, Inc., Chicago, IL).

RESULTS

Participant Characteristics

AA and CA had comparable age (30.9 ± 0.8 vs. 28.3 ± 0.8) and male to female ratio

(female: 47% vs. 55%), respectively. Annual household income did not differ by ethnicity ($p =$

ns), and among all participants, 18 AA (19.8%: 6 females, 12 males) and 12 CA (23.5%: 5

females, 7 male) were either current smokers or had smoked in the past.

Cardiovascular Fitness (VO$_{2max}$)

Fitness, or VO$_{2max}$, was significantly lower in AA men and women relative to CA. Mean

VO$_{2max}$ values for AA men and women were 42.0 ± 1.5 and 32.3 ± 1.3 ml•kg^{-1}•min^{-1},

respectively as compared to 46.5 ± 1.7 for CA men and 38.0 ± 2.0 ml•kg^{-1}•min^{-1} for CA women.

Figure 1 presents ethnic-specific distributions of fitness by three categories: low-fair, average,

and good-high, adjusted for age and gender. Fitness testing indicated suboptimal cardiovascular

health among the majority of our AA population: 57.1% were classified as low to fair fitness and

only 20.9% fell within the good to high categories. In contrast, only 31.4% of our CA were

classified as low-fair fitness and 39.2% fell within the good-high category.

Cardiovascular Disease Risk Factors

All anthropometric measures differed by fitness levels for CA and AA. In CA, body weight,

percent body fat, BMI, waist and hip circumference increased significantly with decreasing

fitness, whereas fasting insulin, HOMA were significantly increased only in the low to fair

category (Table 1). Systolic and diastolic blood pressures were significantly increased in the low-

fair category only in comparison to good-high category.

A dose dependent fitness response was not observed in AA: those in the average and good-high groups did not differ from each other with respect to anthropometric measures, but these two groups had favorable measurements compared to the low-fair category. Blood pressure and fasting insulin were lower in the good-high group compared to low-fair group.

Triglycerides, HDL, and CRP differed between AA and CA: AA had significantly lower triglycerides and CRP but higher HDL compared to CA. In addition, as expected, the higher fitness group had lower triglycerides and CRP and higher HDL relative to the low fitness group. Furthermore, for CA, CRP was significantly lower in the highest as compared to the other two fitness group, whereas for AA, the low-fair differed from both average and good-high groups. Cholesterol, LDL, and non-HDL did not differ by fitness, or ethnicity.

Figure 2 presents the proportion of CA and AA, respectively, who met the criteria for CVD risk within the lowest and highest fitness categories. CVD risk factors that did not differ by fitness in AA included total cholesterol, LDL, non-HDL, triglycerides, fasting glucose, and pre-hypertension. Importantly, total cholesterol, LDL, non-HDL and triglycerides predicted CVD risk in less than 5% of AA in the low-fair fitness category as compared to over 18% of CA. Over 50% of CA and AA (range 55 to 93.8%) meeting the HDL, pre-hypertension, CRP, percent body fat, and BMI criteria for CVD risk were of low-fair fitness. In contrast, 56.3% and 73.3% of CA meeting triglycerides and waist circumference criteria, respectively, were in low-fair fitness as compared to 1.9% and 44.0% of AA.

HOMA, a surrogate of insulin resistance, was also used to identify CVD risk: 75% of CA and 57.7% of AA in the low-fair fitness category were at risk as compared to 5% of CA and 21.2% of AA in the highest fitness category. When the total number of risk factors was calculated, AA and CA in highest fitness category (AA: 2.4 ± 0.5 and CA: 2.5 ± 0.5) had

significantly fewer risk factors for CVD than those in the lowest fitness group (AA: 5.1 ± 0.3 and CA: 8.0 ± 0.5). Although, the number of risk factors increased with decreasing fitness, AA in the low-fair group had significantly fewer risk factors than CA, which supports the importance of adding fitness as a factor in AA to identify persons at risk. Despite excluding persons with hypertension and diabetes from this study, 68.8% of CA and 61.9% of AA were pre-hypertensive, and 34.0% of CA and 45.8% of AA had HOMA values above the level associated with increased risk of CVD (32).

Stepwise linear regression analysis was used with the variables specified in Table 1 to identify the most critical factors contributing to fitness in AA and CA. Initial correlation analyses are reported in Table 2 and the regression analysis is presented in Table 3. Interestingly, no lipid parameter was associated with fitness in either AA or CA groups, whereas CRP was negatively related to fitness in both groups. In addition, CRP was positively associated with all measures of obesity for both CA and AA (Data not shown). Table 3 shows that percent body fat was the most important risk factor associated with fitness for AA and CA, followed by fasting blood glucose and diastolic blood pressure for CA, and CRP for AA.

DISCUSSION

It is well known that higher levels of cardiovascular fitness are associated with lower CVD risk in men and women (4, 13, 17, 34, 37, 38). The studies on which this evidence is based come primarily from samples of predominantly educated CA men and women (1, 4). No comparable normative data are available for AA. In fact, most fitness data for AA have been derived from submaximal tests (38), average maximal MET levels (22), self-reported questionnaires (17), or measured on smaller numbers of overweight and obese individuals at risk for CVD (13). In the present study, we quantified cardiovascular fitness in a sample of apparently "healthy" AA men

and women and found that cardiovascular fitness is low in over half of our sample and inversely related to other factors indicative of CVD risk. We also found that lipid profiles were not associated with fitness, but CRP was inversely related to fitness. The most important indicator of fitness was percent body fat: 93% and 82.4% of obese of CA and AA, respectively, were in the very below average to average fitness categories. Clearly low fitness is one reason AA are at high risk for CVD.

The importance of physical activity and regular exercise for lowering CVD morbidity and mortality has been recognized for many years (4, 5, 20). Although Gaillard et al. (13) have noted the importance of fitness in CVD risk in overweight and obese AA women with hypertension and other multiple CVD risk factors, very little is known about the fitness levels of healthy AA and how fitness relates to CVD risk. In the present study, only 20% of our AA were in the good-high categories as defined by the American College of Sports Medicine (1), and those individuals had comparatively few risk factors for CVD. In contrast, the other 80% had multiple risk factors, with an average of five risk factors. In addition to percent body fat and CRP levels, we also found a strong negative association between fitness and fasting insulin and HOMA: fasting insulin and HOMA were significantly higher in persons of low to fair fitness.

Interestingly, no lipid parameter was associated with fitness in AA, yet physicians often use lipid profiles as indicators of CVD risk. In this apparently healthy population of AA, the current NCEP guidelines for lipid profiles would not have triggered any treatment recommendations by a physician. Because other studies have also questioned the value of lipid profiles in AA, the relation between lipid profiles and CVD risk in AA is unclear (7, 13, 31). Few studies have actually examined how current lipid criteria predict CVD risk in AA and whether lipoprotein parameters change as a function of regular exercise. In one study the only lipid parameter to

change after young and middle-aged, initially sedentary, AA and CA men and women underwent a moderate-intensity exercise was HDL, and it increased only moderately in normolipidemic subjects (23) Thus, the relation between lipids and aerobic fitness remains unclear in AA, but heredity may be important in determining how much exercise can modify lipid profiles (35). This too may be ethnic-specific. Just as selected risk factor criteria differ for men and women, certain criteria may require ethnic-specific cut-points, if they are to be sensitive and specific early indicators of CVD.

Another important risk factor for CVD is CRP. Some studies suggest CRP is a reliable predictor of CVD because cardiovascular mortality is associated with elevations in CRP (6, 12, 27, 33). It has also been reported that CRP differs by ethnicity, with AA women having higher levels (18, 22). However, Miller et al. (29) reported CRP levels were lowest in persons of African origin compared with CA and South Asians. In the present study, CRP was associated with fitness in both ethnic groups, but AA had lower CRP values than CA at the same level of fitness. That CRP also was negatively related to fitness is consistent with previous studies (2, 21, 22).

This study has several limitations. First, participants in this study met restrictive inclusion/exclusion criteria, which may limit the generalizability of the results. Nevertheless, it is clear from our results that interventions to improve fitness are important and will be beneficial in minimizing CVD mortality and morbidity among healthy AA men and women. Our data strongly support the effort by the American College of Sports Medicine and various other organizations that "exercise prescription should become a standard of practice for organized medicine" (36), but also suggest that exercise prescription should be used as a preventive measure, before clinical disease signs are apparent. Another limitation relates to sample size: we had only 91 AA and

57% of those were in the low-fair fitness and only 20.8 were in the good-high group. Thus our sample was skewed towards low fitness. Additionally, we categorized into groups based on the upper and lower 30 percentile values for age and gender (1), but these normative data are derived primarily from CA men and women and may not be appropriate for AA. It has been suggested that AA have lower VO_{2max} values because of reduced muscle oxidative capacity (16). Lastly, we had only one single value for CRP, our only measure of inflammation. Stigant et al. (39) have shown that CRP varies over the short term and thus our single CRP values must be interpreted with caution, despite the clear association between CRP and CVD risk (10, 40)

In summary, we measured cardiovascular fitness, or VO_{2max}, in apparently healthy AA and found that 57% fell within the low-fair fitness group. It is likely less healthy AA would have lower fitness levels and perhaps, be more vulnerable to CVD than our participants. The primary measures negatively associated with fitness - percent body fat, body weight, waist and hip circumference, fasting insulin, HOMA, and CRP - are all risk factors for CVD. In contrast, lipid profiles, in particular triglycerides, were not related to fitness in AA. To identify AA at greatest risk for CVD, fitness should be included as a risk factor. The new national effort, "Exercise is Medicine®", spearheaded by the American College of Sports Medicine, asking physicians worldwide to prescribe physical activity to their patients. This effort must target underrepresented minorities, in particular AA, because they are at greatest risk, and promoting regular physical activity and exercise for improved fitness is essential for reducing health disparities. Also, increasing awareness of the importance of fitness for CVD risk may be critical for AA. Lastly, future research focusing on approaches for encouraging AA to adopt and maintain more physically active lifestyles is needed.

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FIGURE LEGENDS

Figure 1. Cardiovascular Fitness Category by Ethnicity

Note: Percentage of African Americans and Caucasians classified as low to fair, average, and good to high cardiovascular fitness as defined by the American College of Sports Medicine for age and gender.

Figure 2. Percent of African Americans and Caucasians meeting criteria for CVD Risk by Fitness Category

Note: The percent of African Americans and Caucasians who met the criteria for CVD Risk in the low to fair and the good to high fitness categories for total cholesterol, HDL, LDL, triglycerides (TG), non-HDL, BMI, waist circumference (WC), percent body fat (BF), smoking, glucose, CRP, and pre-hypertension (Pre-HT).

Table 1. Physiologic and Metabolic Characteristics of African American and Caucasian Men and Women by Fitness Categories

	Caucasians				African Americans			
	Good/ High (n=20)	Average (n=15)	Fair/Low (n=16)	*P* value	Good/ High (n=19)	Average (n=20)	Fair/Low (n=52)	*P* value
VO$_{2max}$ (ml•kg^{-1}•min^{-1})	51.5 ± 1.4	42.3 ± 1.4	31.5 ± 1.2	<0.001	50.7 ± 1.6	41.4 ± 0.9	29.8 ± 0.8	0.001
Weight (kg)	69.6 ± 3.2[b,c]	85.6 ± 3.9[a,c]	99.3 ± 3.9[a,b]	<.001	73.4 ± 3.2[c]	72.9 ± 3.2[c]	84.7 ± 2.3[a,b]	=.003
Body Mass Index	23.4 ± 0.7[b,c]	28.0 ± 1.1[a,c]	32.3 ± 0.9[a,b]	<.001	24.8 ± 0.7[c]	25.0 ± 0.8[c]	29.4 ± 0.6[a,b]	<.001
Body Fat %	23.4 ± 1.6[b,c]	30.1 ± 2.2[a,c]	38.7 ± 1.6[a,b]	<.001	26.2 ± 1.5[c]	28.1 ± 1.7[c]	34.9 ± 1.1[a,b]	<.001
Waist Circumference (cm)	75.6 ± 1.9[b,c]	90.2 ± 3.6[a,c]	102.3 ± 2.4[a,b]	<.001	80.7 ± 2.1[c]	80.8 ± 2.5[c]	91.5 ± 1.6[a,b]	<.001
Hip Circumference (cm)	97.2 ± 1.5[b,c]	108.7 ± 2.6[a,c]	118.9 ± 2.2[a,b]	<.001	99.2 ± 2.0[c]	101.3 ± 1.8[c]	110.6 ± 1.2[a,b]	<.001
Systolic (mm Hg)	119 ± 2.5[c]	123 ± 3.1	130 ± 2.0[a]	=.016	118 ± 2.5[c]	126 ± 2.5	126 ± 1.8[a]	=.039
Diastolic (mm Hg)	63 ± 1.7[c]	67 ± 1.3[c]	74 ± 2.2[a,b]	<.001	64 ± 1.6[c]	68 ± 2.1	70 ± 1.3[a]	=.031
Fasting Glucose (mM)	5.2 ± 0.2	5.4 ± 0.2	5.4 ± 0.1	ns	4.9 ± 0.1	5.4 ± 0.2	5.2 ± 0.1	ns
Fasting Insulin (µU/mL)	6.2 ± 0.4[c]	9.4 ± 1.5[c]	16.4 ± 2.3[a,b]	<.001	8.0 ± 1.0[c]	10.6 ± 0.8	14.0 ± 1.0[a]	<.001
HOMA	1.4 ± 0.1[c]	2.2 ± 0.3[c]	4.5 ± 0.8[a,b]	<.001	1.8 ± 0.3[b,c]	2.5 ± 0.2[a]	3.3 ± 0.3[a]	<.001
CRP (mg/L)	0.9 ± 0.3[b,c]	3.2 ± 1.4[a]	3.0 ± 0.6[a]	<.001	1.0 ± 0.3[c]	0.4 ± 0.1[c]	2.6 ± 0.4[a,b]	<.001
Total Cholesterol (mg/dL)	150 ± 8.9	151 ± 6.0	164 ± 8.5	ns	154 ± 7.4	156 ± 4.7	157 ± 3.1	ns
Triglycerides (mg/dL)	83 ± 7.5	109 ±14.4	140 ± 17.8	ns	52 ± 4.5	73 ± 12.3	69 ± 5.9	ns
HDL (mg/dL)	46 ± 2.4	40 ± 3.3	40 ± 2.5	ns	53± 3.4	48 ± 2.3	45 ± 1.7	ns
LDL (m/dL)	88 ± 7.4	90 ± 6.8	95 ± 8.4	ns	91 ± 6.7	93 ± 4.3	98 ± 3.0	ns
Non-HDL (mg/dl)	104 ± 7.6	112 ± 7.1	123 ± 9.1	ns	101 ± 7.3	108 ± 5.4	112 ± 23.5	ns

[a]: The group is significantly different from the Good/High Group
[b]: The group is significantly different from the Average Group
[c]: The group is significantly different from the Fair/Low Group

Table 2. Correlational Analyses between VO_{2max} and Cardiovascular Risk Factors

	VO$_{2max}$ (ml•kg^{-1}•min^{-1})	
	Caucasians	African Americans
Weight (kg)	-0.411**	-0.187
Body Mass Index	-0.606***	-0.482***
% Body Fat	-0.851***	-0.700***
Waist Circumference (cm)	-0.605***	-0.334**
Hip Circumference (cm)	-0.749***	-0.534***
Systolic (mm Hg)	-0.114	-0.107
Diastolic (mm Hg)	-0.368**	-0.243*
Fasting Glucose (mM)	-0.043	-0.080
Fasting Insulin (µU/mL)	-0.566***	-0.384***
HOMA	-0.565***	-0.368***
CRP (mg/L)	-0.472***	-0.461***
Total Cholesterol (mg/dL)	-0.193	0.033
Triglycerides (mg/dL)	-0.253	-0.002
HDL (mg/dL)	-0.005	0.061
LDL (m/dL)	-0.038	0.029
Non-HDL (mg/dl)	-0.167	0.018

* *p* < .05; ** *p* < .001; *** *p* < .001

Table 3. Hierarchical Multiple Linear Regression Analysis for
Cardiovascular Fitness and Contributing Factors

VO$_{2max}$	R	R^2	R^2 Change	B
Caucasians				
% Body Fat	.873***	.762***	.762***	-.873***
% Body Fat	.899***	.806***		-.878***
Fasting Glucose			.047**	-.217**
% Body Fat	.910***	.829***		-.833***
Fasting Glucose				-.195**
Diastolic BP			.020*	-.151*
African Americans				
% Body Fat	.701***	.491***	.491***	-.701***
% Body Fat	.738***	.542***		-.589***
CRP			.053**	-.253**

*$p < .05$; ** $p < .001$; *** $p < .001$

Figure 1.

Figure 2.